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ELECTRICAL STIMULATION OF POINTS IN THE FOREBRAIN AND MIDBRAIN

THE RESULTANT ALTERATIONS IN BLOOD PRESSURE

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There has been a great deal of interest in recent years in the vegetative centers of the hypothalamus. Various investigators [1] have stimulated this region and reported dilatation of the pupils, increased blood pressure, contraction of the bladder and increased rate and depth of respiration as well as effects on gastro-intestinal peristalsis and secretion of sweat, saliva, tears, etc. The localization obtained was not precise, however, and no attempt was made to trace the pathways by stimulation.

An extensive investigation was therefore undertaken in this laboratory into the responses of the hypothalamus to electrical stimulation. During this investigation the brain was explored millimeter by millimeter from a level close to the junction of the olfactory bulb and tract as far caudally as a plane through the inferior colliculi dorsally and the middle of the pons ventrally. The Horsley-Clarke stereotaxic instrument was used to orient the electrodes. By stimulation of large numbers of points and identification of every point in stained sections of the brain accurate localization was obtained. Brief reports on the results of this investigation have been published.[2]

The present paper will deal in detailed fashion with the location of the points in the interior of the forebrain and midbrain which on stimulation yield changes in the blood pressure. In this series fifty cats were employed, and 7,700 points in the brain were stimulated.

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1. (*a*) Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: I. Zwischenhirnbasis und Halssympathicus, Arch. f. d. ges. Physiol. **129**:138, 1909. (*b*) Beattie, J.: Hypothalamic Mechanisms, Canad. M. A. J. **26**:400, 1932.

2. (*a*) Kabat, H.; Ranson, S. W., and Magoun, H. W.: Electrical Stimulation of the Hypothalamus, Proc. Soc. Exper. Biol. & Med. **31**:541, 1934. (*b*) Ranson, S. W.; Kabat, H., and Magoun, H. W.: Autonomic Responses to Electrical Stimulation of the Hypothalamus, Preoptic Region and Septum, Arch. Neurol. & Psychiat. **33**:467 (March) 1935.

METHODS

The animals were given intraperitoneal injections of a small dose of pentobarbital sodium, from 15 to 18 mg. per kilogram of body weight. A tracheal cannula was then introduced, and supplementary ether was given when necessary to maintain light anesthesia. The lower portion of the abdomen and pelvis were opened, and a cannula was introduced into the bladder, following which the cat was turned over, the calvarium exposed, an area of bone 15 mm. square removed and the Horsley-Clarke instrument fastened to the head. A complete description of the instrument and of the manner in which it is used can be found in papers by Horsley and Clarke [3] and by one of us (S. W. R.).[4]

The cat was then placed on its back and left in that position for the remainder of the experiment. A cannula was introduced into the carotid artery and connected to a mercury manometer which recorded on a kymograph, on which simultaneous records of intravesical pressure and respiration were taken. Each stimulus was numbered both on the kymographic record and on a written record, which contained, in addition, the Horsley-Clarke coordinates for the point stimulated and notes on any changes in the pupils and movements of striated muscles which were observed.

The stimulating current was provided by a Harvard inductorium having one dry cell in the primary circuit with the secondary coil set as a routine at 9 cm. The bipolar electrodes consisted of two lengths of enameled nichrome wire cemented together and entirely insulated except at the tips, which were separated by from 0.2 to 0.3 mm., so that only the very small area of brain tissue immediately surrounding the end of the electrode was stimulated. For stimulation of the frontal lobe, electrodes were employed which were separated at the tips by 1 mm.

The procedure used in stimulating follows: The electrode was inserted vertically into the brain in or near the midline to the desired depth. The stimulus was applied for approximately 10 seconds. The kymograph was run during stimulation and for some seconds both before and afterward, so that a record was obtained of the resting state, the response to stimulation and any after-effects that might be produced. Following this, the electrode was moved down 1 mm., fixed in place and stimulation carried out, a short time being allowed between stimuli. This was repeated, the electrode being moved down, millimeter by millimeter, and a stimulus applied at each stop until the electrode was as deep as was desired. The electrode was then withdrawn, moved 1 mm. laterally and inserted once more, points being stimulated at every millimeter on the way down in the manner described. Usually one or two punctures were made on one side of the midline, and then the electrode was moved to the opposite side and punctures were made at each millimeter moving laterally. This was repeated until from five to twelve punctures had been made and that particular rostrocaudal level of the brain stem thoroughly explored. Some punctures were less deep than others, having been stopped at points which yielded especially good reactions, and hence a variable number of points were stimulated along the different punctures. At the completion of a transverse row of punctures the electrode was moved 2 mm. caudally, and this level was explored in the same way as the more rostral one. From three to five such levels were explored in each cat, 175 being the average number of points stimulated in one cat. By stimulating at

3. Horsley, V., and Clarke, R. H.: The Structure and Functions of the Cerebellum Examined by a New Method, Brain **31**:45, 1908.

4. Ranson, S. W.: On the Use of the Horsley-Clarke Stereotoxic Instrument, Psychiat. en neurol. bl. [**38**:] 534, 1934.

odd-numbered levels, such as 11, 9, 7 and 5 mm., anterior to the zero point of the instrument in one cat and stimulating at even-numbered levels, such as 12, 10, 8 and 6, in the next cat, each millimeter from A 23 to A1 was thoroughly explored.

After the experiment was completed, wires were placed with the aid of the instrument in the brain in front of and behind the explored area as a guide to indicate the proper plane of section. The cat was killed with ether, and formaldehyde was injected into its head. When the brain was hard it was removed, and a block containing the area stimulated was excised, embedded and cut, in planes corresponding to those of the punctures, into serial sections, which were stained by Weil's method.

The punctures appeared as thin black lines of hemorrhage in the sections. After the shrinkage was determined, measurements were made with an ocular micrometer from the lowest point of each puncture, so that every point stimulated was localized. Any point which was definitely marked by stopping the puncture when an especially good reaction was obtained served as a check on these measurements. The points were mapped on outline drawings of the sections. By a study of the corresponding sections of a brain of a normal cat in which alternate sections were stained with cresyl violet and by Weil's method, the relation of the points to the various nuclear groups was determined. The kymographic records were analyzed, and the responses were indicated in symbols on the drawings close to the dots marking the points the stimulation of which yielded those responses. Finally, the points stimulated in all the cats were plotted on one complete series of drawings of sections of the brain stem, in which form the data could readily be analyzed.

RESULTS

Blood Pressure.—When a pressor point was stimulated, the blood pressure rose rather sharply after a latent period of approximately 1 second. Karplus and Kreidl [5] reported a similar latent period for the response of the blood pressure to stimulation of the hypothalamus. The pressure rose steadily during stimulation and not infrequently reached its peak before the end of the stimulus. As a rule there was no secondary rise. The pressure began to decline as soon as the stimulus was discontinued, and sometimes it fell below the previously prevailing level (fig. 1).

Stimulation of depressor points resulted in definite falls in the blood pressure, which, however, were not as pronounced as were the rises. The latent period was short, but the pressure did not return to its former level until some time after cessation of stimulation (fig. 2).

The changes in the blood pressure have been arbitrarily subdivided according to magnitude. The average marked rise amounted to from 35 to 40 mm. of mercury. The blood pressure sometimes increased as much as 98 mm. during stimulation. In the illustrations marked rises (more than 20 mm.) are indicated by solid circles and moderate ones

5. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: VII. Ueber Beziehungen der Hypothalamuszentren zu Blutdruck und inneren Sekretion, Arch. f. d. ges. Physiol. **215**:667, 1927.

(from 10 to 20 mm.) by crosses, while the points which gave slight rises (less than 10 mm.) are not indicated. Falls in the blood pressure are indicated by solid triangles, which symbol designates slight falls (from 5 to 10 mm.) as well as moderate ones (from 10 to 20 mm.). No drop in blood pressure of more than 20 mm. was observed.

Very localized stimulation is possible with the method employed. Stimulation of the lateral hypothalamic area causes a marked dilatation of the pupils, but when the electrode is moved only 1 mm. deeper—into the optic tract—stimulation yields marked constriction of the pupils. The accuracy of the method is well illustrated by an observation on the somatic movements which resulted from stimulation in cat 22. Of 64

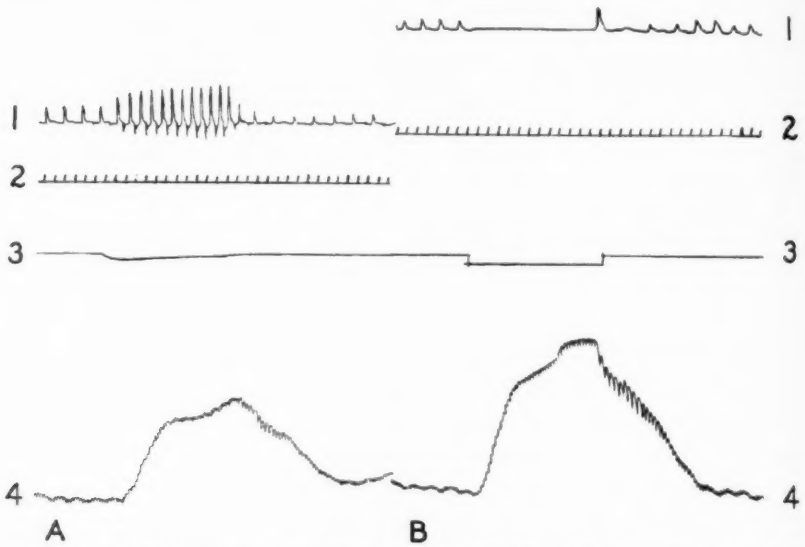

Fig. 1.—Kymographic records showing rises in the blood pressure. Note the increase in the depth and the decrease in the rate of the pulse immediately following cessation of stimulation. *1* indicates respiration; *2*, time in seconds; *3*, signal magnet, and *4*, blood pressure. *A* is a record produced by stimulation of the lateral part of the hypothalamus. Note the increased rate and depth of respiration. *B* is a record produced by stimulation of the mesencephalic tegmentum. Note the respiratory inhibition.

points stimulated in the supra-optic region, only 2 yielded rhythmic "spitting" [6] (a mimetic response), and these were found on microscopic examination to be symmetrically placed on each side in the subfornical component of the medial bundle of the forebrain.

6. "Spitting" is a type of mimetic response such as a cat makes when confronted with a dog and consists of opening of the mouth and baring of the teeth with greatly increased amplitude of respiration and forced expiration.

Extraneous factors, such as fatigue, the p_H of the blood, the depth of anesthesia and the trauma occasioned by numerous punctures in the brain, affect the magnitude of the response of the blood pressure. In order to minimize these factors in a comparison of the responsiveness of different regions, each region of the brain was stimulated many times in a number of different cats, in some cases at the beginning of the experiment and in others toward the end, depending on the rostrocaudal level of the first row of punctures.

Rises in Blood Pressure Obtained on Stimulation of Points in the Telencephalon.—A significant rise in the blood pressure was a rare occurrence in response to stimulation of the telencephalon, and no region

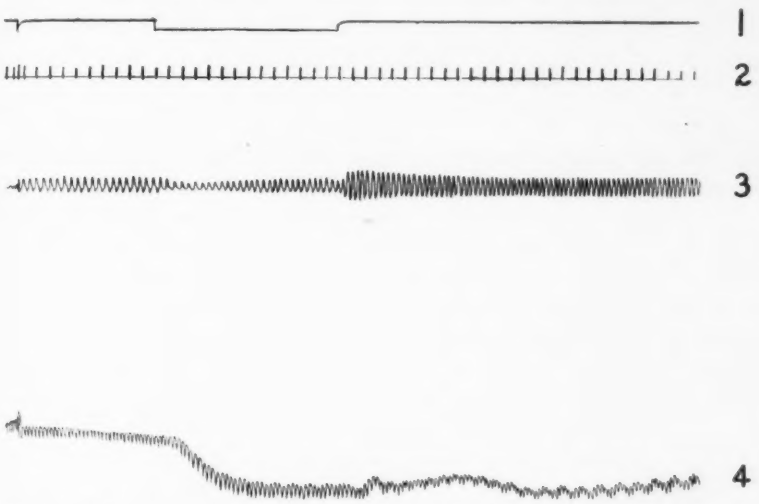

Fig. 2.—A kymographic record showing a fall in the blood pressure (*4*) and a decrease in the amplitude of respiration (*3*) produced by stimulation in the neighborhood of the anterior commissure. Note the "vagus effect" on the pulse during stimulation. *1* indicates signal magnet, and *2*, time in seconds.

gave consistent reactions of any magnitude (figs. 3 and 4 *A*). A few marked, occasional moderate and a number of slight responses were obtained on stimulation of the internal capsule. These changes in the blood pressure were probably secondary to the muscular movements resulting from stimulation. At the level of the crossing of the anterior commissure marked increases in arterial pressure, accompanied by struggling, rhythmic stepping or spitting, were produced by stimulation of the most ventral portion of the medial preoptic area (fig. 4 *A*). Either the blood pressure center in the hypothalamus extends rostrally to the level of the anterior commissure or the reactions are due to a spread of current to the anterior part of the hypothalamus. A spread

of current would explain the concentration of points yielding moderate rises in blood pressure in the lateral preoptic area at its junction with the lateral hypothalamic area. Occasional moderate rises and many slight ones resulted from stimulation of the bed nuclei of the stria terminalis and of the anterior commissure, as well as of the medial and lateral preoptic areas. It is noteworthy that excitation of the corpus striatum caused no rise in the blood pressure.

Falls in Blood Pressure Obtained on Stimulation of Points in the Telencephalon.—Slight or moderate falls in the blood pressure were produced by stimulation of a localized area at every level of the telencephalon that was explored. The response was obtained from the medial portion of the white center of the rostral part of the frontal lobe and was traced along the band of fibers medial to the lateral ventricle and through the septum pellucidum and the medial preoptic area to the caudal end of the telencephalon (figs. 3 to 4 *A*).

At the most rostral level studied, close to the junction of the olfactory bulb and tract, depression of the blood pressure was obtained on stimulation of the portion of the white center of the frontal lobe adjacent to the gyrus genualis and was sometimes observed during stimulation of the gyrus orbitalis. From here, the reactive zone could be traced caudally through the medial white center (fig. 3 *A*). At a level where the lateral ventricle splits the medial white center, most of the responsive points were localized in the band of myelinated fibers medial to the ventricle, and a few were placed in the gyrus genualis (fig. 3 *B*). The fall in the blood pressure could be traced caudally through this band of fibers to the genu of the corpus callosum.

Exploration in a plane through the genu of the corpus callosum (fig. 3 *C*) revealed that the responsive zone was much more extensive, including all of the region medial to a line drawn vertically through the ventral tip of the lateral ventricle from the corpus callosum to the base of the brain. This area contains the genu of the corpus callosum, the caudal end of the gyrus genualis and the gray matter medial and dorsomedial to the olfactory tubercle. Besides, falls in the blood pressure were elicited on stimulation of the gray matter adjacent to the anterior commissure and of the caudate nucleus, especially where it forms part of the wall of the lateral ventricle. More caudally, the reactive area included the septum pellucidum and all of the medial preoptic area down to the base of the brain (fig. 3 *D*). The corpus callosum and the anterior commissure were unresponsive.

Just in front of the crossing of the anterior commissure, numerous moderate and slight falls in the blood pressure resulted from stimulation medial to the anterior commissure, close to the ventral tip of the lateral ventricle and in the dorsal portion of the medial preoptic area.

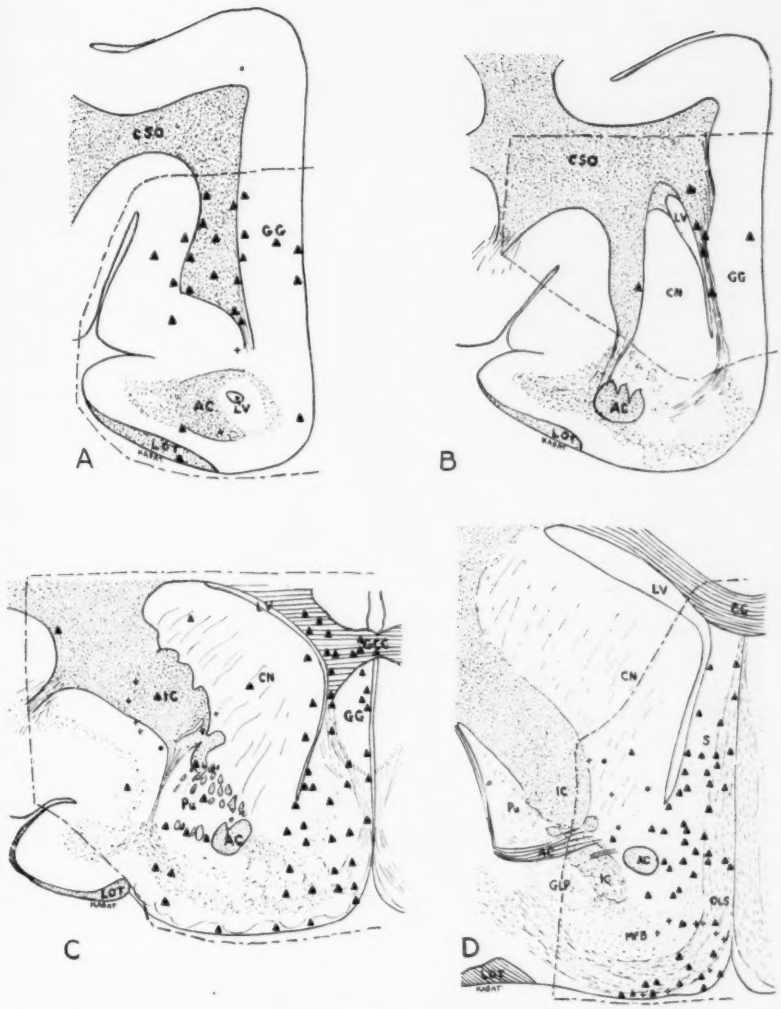

Fig. 3.—*A* represents a section through the most rostral tip of the lateral ventricle. The marked and moderate responses obtained in the two cats which were stimulated in this plane are shown. *B* represents a section through the telencephalon rostral to the genu of the corpus callosum. The marked and moderate responses obtained in the one cat stimulated in this plane are shown. *C* represents a section through the genu of the corpus callosum. The marked and moderate responses obtained in the eight cats stimulated in this plane are shown. *D* represents a section through the septum pellucidum and preoptic area rostral to the crossing of the anterior commissure. The marked and moderate responses obtained in the eight cats stimulated in this plane are shown. In this and the following illustrations the triangles indicate falls in blood pressure; the circles, marked rises, and the crosses, moderate rises. The dotted line delimits the area explored. The abbreviations used in the figure are: *AC*, anterior commissure; *CC*, corpus callosum; *CN*, caudate nucleus; *CSO*, centrum semiovale; *GCC*, genu of the corpus callosum; *GG*, gyrus genualis; *GLP*, globus pallidus; *IC*, internal capsule; *LOT*, lateral olfactory tract; *LV*, lateral ventricle; *MFB*, medial bundle of the forebrain; *OLS*, olfactoseptal fibers; *Pu*, putamen, and *S*, septum pellucidum.

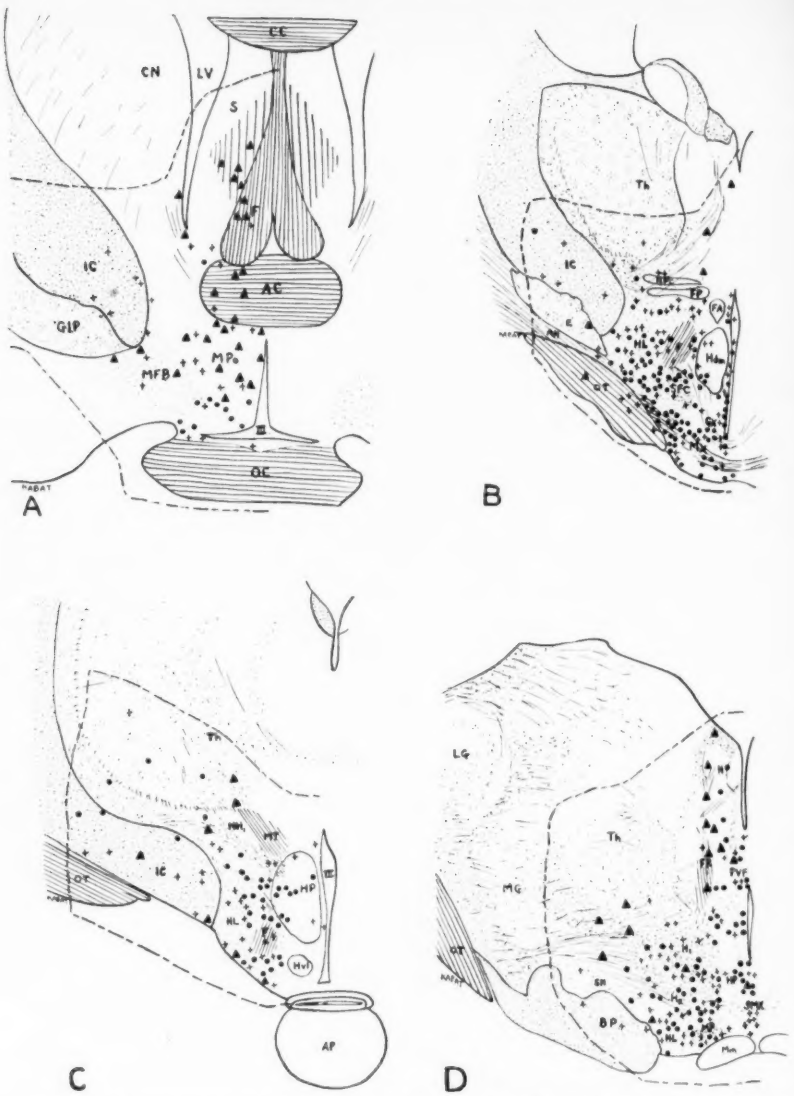

Fig. 4.—*A* represents a section through the telencephalon in a plane through the crossing of the anterior commissure. The marked and moderate responses of the eleven cats stimulated in this plane are shown. *B* represents a section through the diencephalon in a plane through the supra-optic commissures. The marked and moderate responses of the ten cats stimulated in this plane are shown. *C* represents a section through the diencephalon at a level just in front of the mamillary bodies. The marked and moderate responses of the seven cats stimulated in this plane are shown. *D* represents a section through the caudal part of the mamillary bodies. The marked and moderate responses of the nine cats stimulated in this plane are shown. The abbreviations used in this illustration are: *AC*, anterior commissure; *AN*, ansa lenticularis, *AP*, anterior lobe of the pituitary; *BP*, basis pedunculi; *CC*, corpus callosum; *CN*, caudate nucleus; *E*, entopeduncular nucleus; *F*, fornix; *FA*, nucleus filiformis anterior; *FP*, nucleus filiformis principalis; *FR*, habenulopeduncular tract; *GLP*, globus pallidus; *GX*, Ganser's commissure, H_1, H_1 field of Forel; H_2, H_2 field of Forel; *H*, habenula; *Hdm*, nucleus hypothalamicus dorsomedialis; *HL*, lateral hypothalamic area; *HP*, nucleus hypothalamicus posterior; *Hpc*, nucleus hypothalamicus parvocellularis; *Hvl*, nucleus hypothalamicus ventrolateralis; *IC*, internal capsule; *LG*, lateral geniculate body; *LV*, lateral ventricle; *MFB*, medial bundle of the forebrain; *MG*, medial geniculate body; *Mm*, medial mamillary nucleus; *MP*, mamillary peduncle; *MPo*, medial preoptic area; *MT*, mamillothalamic tract; *MX*, Meynert's commissure; NH_1, nucleus of H_1 field of Forel; *OC*, optic chiasm; *OT*, optic tract; *PVF*, periventricular fibers; *S*, septum pellucidum; *SFC*, subfornical component of the medial bundle of the forebrain; *SMX*, supramamillary commissure; *SN*, substantia nigra; *Th*, thalamus, and *III*, third ventricle.

Some responses were also evoked on stimulation of the anterior commissure and the lateral preoptic area. Stimulation of the septum pellucidum and the ventral part of the medial preoptic area had no effect.

In a plane through the crossing of the anterior commissure (fig. 4*A*) falls in the blood pressure were obtained on stimulation of the ventral part of the septum, the anterior commissure and the dorsal portion of the medial preoptic area. A few stimuli in a small segment of the fornix were effective.

Even in the regions which have been outlined as giving depressor reactions, large numbers of stimuli had no effect or resulted in slight rises. Stimulation of these reactive regions caused no somatic movements or changes in the size of the pupils but did result in decreases of varying degree in the rate and amplitude of respiration. Vigorous contractions of the bladder were elicited on stimulation of the septum pellucidum and of the medial preoptic area.

Certain structures seem to be responsive only because of a spread of current to adjacent areas. This is true of the portion of the caudate nucleus close to the lateral ventricle. The falls in the blood pressure elicited from the crossing of the anterior commissure were probably due to a spread of current to the bed nucleus, since stimulation of the anterior commissure in front of its crossing was ineffective. Stimulation of the fornix just behind the anterior commissure caused a decrease in the blood pressure. But only a small segment of the fornix was reactive more rostrally, and in the diencephalon stimulation of the fornix never yielded a fall in the blood pressure. It is probable that a spread of current accounts for the responsiveness of this tract at one level and not at others.

The regions of the telencephalon which yielded falls in the blood pressure on stimulation very infrequently included: the internal capsule, the area insularis granularis, the olfactory tubercle, the claustrum, the corpus callosum caudal to its genu, the optic chiasma, the lateral preoptic area and the medial bundle of the forebrain. In general, wherever the caudate and lentiform nuclei were explored they were found to be unresponsive.

Rises in Blood Pressure Obtained on Stimulation of Points in the Diencephalon.—In contrast to the effects of excitation of the telencephalon, marked elevations of the blood pressure were consistently elicited on stimulation of a localized area of the hypothalamus at every level explored. The response could be traced through the hypothalamus from the level of the optic chiasma to the caudal end of the mamillary bodies and from there, without a break, into the mesencephalon (figs. 4*B* to *D*). The most responsive structures were the subfornical com-

ponent of the medial bundle of the forebrain, the supra-optic commissures, the lateral hypothalamic area and medial bundle of the forebrain, the perifornical nucleus, the hypothalamicotegmental fibers, the H_1 field of Forel, the supramamillary commissure and the periventricular fibers. In these regions practically every stimulus resulted in a significant rise in the blood pressure. A detailed description and an atlas of the anatomic structures in the diencephalon can be found in a paper by Ingram, Hannett and one of us (S. W. R.).[7] Reference will be made in the following paragraphs to some of the figures in this atlas.

At the level of the optic chiasma the points which yielded rises in the blood pressure on stimulation were concentrated in and around the subfornical component of the medial bundle of the forebrain [8] and were also located in the lateral part of the nucleus supra-opticus diffusus and the ventromedial part of the anterior hypothalamic area. Moderate rises were obtained on stimulation of the gray matter surrounding the fornix and occasionally on stimulation of the midline of the hypothalamus and the lateral hypothalamic area (figs. 2 and 3 in reference 7).

Stimulation in a plane through the supra-optic commissure (fig. 4*B*) was effective in provoking marked increases in the blood pressure from the subfornical component of the medial bundle of the forebrain, the ventral part of the lateral hypothalamic area, the supra-optic nucleus and the commissures of Ganser and Meynert as well as the gray matter through which these commissures course. A large percentage of the stimuli in the midline close to the base were effective, indicating a possible crossing of impulses at this level. Many moderate and some marked responses were obtained on stimulation of the fornix and the gray matter just dorsal to it, the dorsal part of the lateral hypothalamic area, the lateral half of the nucleus hypothalamicus dorsomedialis and the dorsal portion of the hypothalamus in the midline. The occasional rises in the blood pressure which were recorded on stimulation of the optic tract close to Meynert's commissure were evidently the result of a spread of current.

At a level just behind the supra-optic commissures (figs. 6 and 7 in reference 7) marked rises in the blood pressure were elicited on stimulation of the ventral part of the lateral hypothalamic area, the perifornical nucleus and the fibers running transversely between the optic tract and the entopeduncular nucleus; these responsive fibers may be those of the ansa lenticularis or of Meynert's commissure. The

7. Ingram, W. R.; Hannett, F. I., and Ranson, S. W.: Topography of the Nuclei of the Diencephalon of the Cat, J. Comp. Neurol. **55**:333, 1932.

8. Krieg, W. J. S.: The Hypothalamus of the Albino Rat, J. Comp. Neurol. **55**:19, 1932.

dorsal portion of the lateral hypothalamic area and the gray matter dorsal to the fornix yielded moderate responses. Stimulation of the nucleus hypothalamicus ventromedialis and of the midline caused no change in the blood pressure.

In a plane through the posterior part of the nucleus hypothalamicus ventromedialis (figs. 8 and 9 in reference 7) the gray matter surrounding the fornix was most responsive. Moderate rises were elicited on stimulation of the lateral part of the lateral hypothalamic area, the medial part of the dorsal hypothalamic area, the lateral portion of the nucleus hypothalamicus ventromedialis and the midline.

At the level of the rostral part of the nucleus hypothalamicus posterior (figs. 10 and 11 in reference 7) the points yielding marked responses were localized in the lateral hypothalamic area, the fornix and the perifornical nucleus. Some marked and moderate responses were obtained on stimulation of the ansa lenticularis and the nucleus of the H_1 field of Forel. Stimulation of the posterior hypothalamic nucleus and the dorsal hypothalamic area gave rise to moderate reactions. The midline was unresponsive.

Just rostral to the mamillary bodies (fig. 4*C*) marked rises in the blood pressure were elicited on stimulation of the perifornical nucleus, the ventrolateral portion of the nucleus hypothalamus posterior, through which the hypothalamicotegmental fibers course, and the dorsal part of the lateral hypothalamic area. A few marked reactions were evoked on stimulation of the zona incerta, and many moderate reactions were observed during stimulation of the ventral part of the lateral hypothalamic area.

In a plane through the rostral part of the mamillary bodies (figs. 14 and 15 in reference 7) the responsive region included the lateral hypothalamic area and the part of the mamillothalamic tract adjacent to it. Moderate and occasional marked elevations of blood pressure were provoked by stimulation of the periventricular fibers in the posterior hypothalamic nucleus. The H_1 field of Forel and the lateral mamillary nucleus yielded moderate responses.

At the level of the middle of the mamillary bodies the stimuli resulting in a significant rise in the blood pressure were localized in the H_1 and H_2 fields of Forel, the lateral hypothalamic area, the region of the mamillary peduncle and the supramamillary commissure and along the course of the periventricular fibers reaching dorsally almost to the habenula. The posterior hypothalamic nucleus, through which the periventricular fibers pass, was very responsive at this level (figs. 16 and 17 in reference 7).

At the caudal end of the mamillary bodies (fig. 4*D*) the responsive region was the same as that described in the preceding paragraph, except that the medial region through which the periventricular fibers course

was even more reactive. Only moderate rises in the blood pressure were elicited on stimulation of the supramamillary commissure in the midline.

It seems likely that many of the structures from which rises in the blood pressure were obtained are not in themselves concerned in the reaction and are responsive only because fibers belonging to the pressor pathway run through them. In some instances a spread of current may be responsible. For example, a rise in the blood pressure was never evoked by stimulation of the fornix in the telencephalon, so that its responsiveness in the hypothalamus may be ascribed to a spread of current. Similarly, the mamillothalamic tract was unresponsive except where adjacent to the lateral hypothalamic area. Stimulation of the fibers that originate farther forward will not account for the responsiveness of the lateral hypothalamic area, since stimulation of the medial bundle of the forebrain in the telencephalon is ineffective. However, there is a possibility of a new influx of fibers into this bundle in the diencephalon. The responsiveness of the supra-optic nucleus is apparently the result of a spread of current to the reactive region dorsomedial to it.

Portions of the medial hypothalamic nuclei seem to be responsive because of a spread of current to adjacent areas or to fibers that are passing through them. Our method does not furnish conclusive evidence on this point, however. The reactive portions of the posterior hypothalamic nucleus contain either hypothalamicotegmental fibers or periventricular fibers. A spread of current may account for the moderate reactions elicited on stimulation of the dorsomedial, ventromedial and posterior hypothalamic nuclei and of the lateral mamillary nucleus and the dorsal hypothalamic area. The portions of the hypothalamus which were entirely unresponsive include: the nucleus ovoideus, the nucleus filiformis anterior and nucleus filiformis principalis, the nucleus hypothalamicus parvocellularis, the nucleus periventricularis dorsalis, the nucleus mamillaris medialis and the nucleus supramamillaris.

Control stimulation of other diencephalic structures showed the thalamus uniformly unresponsive except along the course of the periventricular fibers at the level of the mamillary bodies. The optic tract and the entopeduncular nucleus were unresponsive. Responses were obtained rather infrequently from the zona incerta and subthalamic nucleus of Luys. Most of the points in the internal capsule and basis pedunculi were unresponsive or yielded slight rises, while moderate responses were seen only occasionally and marked ones infrequently.

Stimulation of the lateral hypothalamus results not only in a marked rise in the blood pressure but also in marked dilatation of the pupils, contraction of the bladder, greatly increased rate and amplitude of respiration and various somatic movements such as struggling and run-

ning from the lateral hypothalamic area and rhythmic spitting from the supra-optic region. There are some who believe that the changes in the blood pressure resulting from stimulation of the hypothalamus are always secondary to activity of the skeletal muscles.[9] In order to discover the relation of somatic movements and changes in respiration to the response of the blood pressure, the hypothalamus was stimulated in two cats which were completely paralyzed by the administration of curare. A marked rise in the blood pressure, contraction of the bladder and dilatation of the pupils were produced, although there was no movement of the striated muscles (fig. 5*A*). These responses in curarized cats were obtained from the subfornical component of the medial bundle of the forebrain in the anterior part of the hypothalamus, from the lateral hypothalamic area and perifornical nucleus in the middle of the hypothalamus and from the lateral hypothalamic area, the H_1 field of Forel, the supramamillary commissure and the periventricular fibers at the level of the mamillary bodies. In one of these cats a rise in the blood pressure of 76 mm. was elicited on stimulation of the lateral hypothalamic area, and repetition of the stimulus at the same point five times in succession gave the same result, although the cat was completely paralyzed. The only point in the internal capsule that was stimulated was unresponsive.

Falls in Blood Pressure Obtained on Stimulation of Points in the Diencephalon.—Very few falls in the blood pressure were evoked by stimulation of the diencephalon. There was some tendency for the points yielding this response to be localized in certain regions, but even in these regions depression of the blood pressure was only an occasional result of stimulation. Rostrally, effective points were found in the inferior thalamic peduncle (fig. 4*B*), the anterior paraventricular nucleus, the external medullary lamina and the region ventromedial to the entopeduncular nucleus (figs. 2 to 5 in reference 7). In the middle of the diencephalon some falls in the blood pressure were produced by stimulation of the region lateral and dorsolateral to the mamillothalamic tract (fig. 4*C*), of the base of the lateral hypothalamus and more rarely of the medial part of the internal capsule and of the midline (figs. 10 to 13 in reference 7). At the level of the mamillary bodies the response was obtained from the habenulopeduncular tract (fig. 4*D*), from the region lateral to the H_1 field of Forel and sometimes from the periventricular fibers and the lateral hypothalamic area.

Rises in Blood Pressure Obtained on Stimulation of Points in the Mesencephalon.—At the caudal end of the diencephalon the structures

9. Leiter, L., and Grinker, R. R.: Rôle of the Hypothalamus in Regulation of Blood Pressure: Experimental Studies, with Observations on Respiration, Arch. Neurol. & Psychiat. **31**:54 (Jan.) 1934.

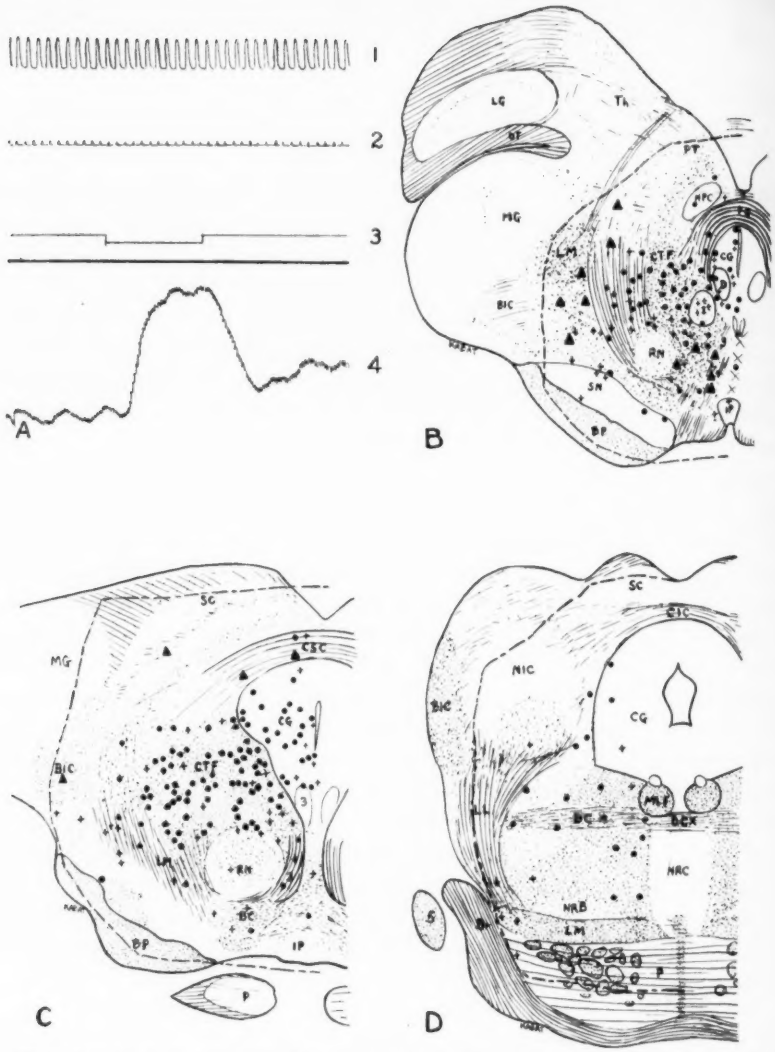

Fig. 5.—*A* is a kymographic record showing a marked rise in the blood pressure (*4*) during stimulation of the lateral part of the hypothalamus in an animal completely paralyzed by means of curare. *1*, indicates artificial respiration; *2*, time in seconds and *3*, signal magnet. *B* represents a section through the posterior commissure. The marked and moderate responses of the six cats stimulated in this plane are shown. *C* represents a section in a plane through the rostral part of the superior colliculi dorsally and the rostral tip of the pons ventrally. The marked and moderate responses of the eight cats stimulated in this plane are shown. *D* represents a section through the inferior colliculi dorsally and the middle of the pons ventrally. The marked and moderate responses of the one cat stimulated in this plane are shown. The abbreviations in this figure are as follows: *BC*, brachium conjunctivum; *BCX*, commissure of the brachium conjunctivum; *BIC*, brachium of the inferior colliculus; *BP*, basis pedunculi; *Br*, brachium pontis; *CG*, central gray matter; *CIC*, commissure of the inferior colliculus; *CSC*, commissure of the superior colliculus; *CTF*, central tegmental fasciculus; *D*, nucleus of Darkshevich; *I*, interstitial nucleus; *IP*, interpeduncular nucleus; *LG*, lateral geniculate body; *LL*, lateral lemniscus, *LM*, medial lemniscus; *MG*, medial geniculate body; *MLF*, medial longitudinal fasciculus; *NIC*, nucleus of the inferior colliculus; *NPC*, nucleus of the posterior commissure, *NRB*, nucleus reticularis of Bechterew; *NRC*, nucleus reticularis centralis; *OT*, optic tract; *P*, pons; *PC*, posterior commissure; *PT*, pretectal area; *RN*, red nucleus; *SC*, superior colliculus; *SN*, substantia nigra; *Th*, thalamus; *3*, oculomotor nucleus or nerve, and *5*, trigeminal nerve.

which yielded rises in blood pressure on stimulation were the lateral hypothalamic area, the H_1 field of Forel, the supramamillary commissure and the periventricular fibers (fig. 4 *D*). From here, the reactive area spread out through the central gray matter and the tegmentum (fig. 5*B* to *D*) and could be traced to the most caudal level explored, which was in a plane through the rostral part of the inferior colliculi dorsally and the middle of the pons ventrally. In the responsive regions practically every stimulus resulted in a significant rise in the blood pressure.

Just behind the mamillary bodies increases in the blood pressure were elicited on stimulation of the periventricular fibers, the medial part of the tegmentum and the substantia nigra. Some responses were also obtained from the lateral part of the tegmentum (figs. 20 and 21 in reference 7).

Exploration at the level of the rostral portion of the posterior commissure revealed that all of the midline between the interpeduncular nucleus and this commissure was very responsive. Stimulation of the tegmentum medial to a line drawn vertically through the medial edge of the basis pedunculi yielded marked and some moderate rises. Some marked reactions were also obtained from the substantia nigra, and moderate ones resulted from stimulation of the lateral part of the tegmentum and the ventrolateral portion of the central gray matter (figs. 22 and 23 in reference 7).

In a plane through the middle of the posterior commissure (fig. 5*B*) every stimulus in the central tegmental fasciculus caused a marked rise in the blood pressure. Marked responses were also evoked on stimulation of the central gray matter in the midline. Excitation of the remainder of the central gray matter and of the tegmentum adjacent to the red nucleus gave rise to moderate and some marked reactions. The substantia nigra and the lateral portion of the tegmentum were in general unresponsive.

Stimulation of the central tegmental fasciculus and of the central gray matter exclusive of the oculomotor nuclei was very effective in a plane through the rostral part of the superior colliculi dorsally and the rostral tip of the pons ventrally (fig. 5*C*). Some marked and moderate responses were obtained from the medial lemniscus and the brachium conjunctivum.

At various levels through the superior colliculi caudal to that just described, the lateral part of the tegmentum as well as the central tegmental fasciculus was very responsive. Marked and moderate rises in the blood pressure were not infrequently elicited on stimulation of the central gray matter. Some responses were obtained from the brachium conjunctivum, while a significant effect was rarely recorded during excitation of the medial lemniscus.

At the most caudal level explored, in a plane through the rostral portion of the inferior colliculi dorsally and the middle of the pons ventrally (fig. 5*D*), the responsive area included the lateral part of the central gray matter, the region between the central gray matter and the nucleus of the inferior colliculi and all of the tegmentum. The small number of responses indicated at this level is explained by the fact that this figure represents the results from only one cat.

We cannot settle the question whether the occasional responses elicited from the medial lemniscus are the result of a spread of current or of stimulation of these ascending fibers. Just as in the telencephalon and diencephalon, stimulation of the fibers of the pyramidal tract gave rise only to occasional moderate and very few marked elevations of the blood pressure. The parts of the mesencephalon and caudal diencephalon which were explored and found to be unresponsive include: the habenular nuclei, the interpeduncular nucleus, the nucleus of Darkshevich, the interstitial nucleus, the posterior commissure, the nucleus of the posterior commissure, the pretectal area, the oculomotor nucleus and nerve, the red nucleus, the superior colliculus, the brachium of the inferior colliculus and the inferior colliculus. Whenever the medial geniculate body was stimulated, it yielded no response.

In general, the regions of the mesencephalon which yielded marked rises in the blood pressure on stimulation also elicited dilatation of the pupils and contraction of the bladder. In addition, a marked increase in rate and depth of respiration as well as vigorous rhythmic spitting was elicited on stimulation of the central gray matter. Stimulation of the tegmentum usually caused a decrease in the rate and depth of respiration or even apnea, together with the so-called tegmental reaction.[10]

Falls in Blood Pressure Obtained On Stimulation of Points in the Mesencephalon.—No definite uninterrupted pathway for depression of the blood pressure could be traced through the mesencephalon. Nevertheless, this response was not infrequently produced by stimulation of certain regions, such as the lateral portion of the tegmentum and the habenula and habenulopeduncular tract (figs. 5*B* to *D*).

At the caudal end of the diencephalon (fig. 4*D*) falls in the blood pressure resulted from stimulation of the periventricular fibers, the habenulopeduncular tract and the region just ventral to the arcuate nucleus. Behind this level the response was elicited from the periventricular fibers, the habenulopeduncular tract, the region of the arcuate and subparafascicular nuclei and the area lateral to the *cntre médian.*

10. Ingram, W. R.; Ranson, S. W.; Hannett, F. I.; Zeiss, F. R., and Terwilliger, E. H.: Results of Stimulation of the Tegmentum with the Horsley-Clarke Stereotaxic Apparatus, Arch. Neurol. & Psychiat. **28**:513 (Sept.) 1932.

In planes through the posterior commissure (fig. 5 *B*) the reactive points were localized in the tegmentum just internal to the medial geniculate body. The responses produced by stimulation of the rostral part of the posterior commissure and of the region medial to the red nucleus were probably the result of a spread of current to the habenulopeduncular tract.

At the level of the rostral end of the superior colliculi dorsally and the rostral tip of the pons ventrally (fig. 5 *C*) depression of the blood pressure was a very infrequent response. Several responses were provoked by stimulation of the commissure of the superior colliculus and the lateral part of the tegmentum.

During exploration farther caudally, some falls in the blood pressure were elicited on stimulation of the central gray matter, especially in the midline. A number of marked falls were obtained on stimulation of the region dorsolateral to the medial lemniscus, and it is of some interest that many of these responses were accompanied by rhythmic spitting. Stimulation of two levels through the superior colliculi and one through the inferior colliculi failed to bring about any falls in the blood pressure (fig. 5 *D*).

Pulse Rate.—In fifteen cats of the series the changes in the pulse rate were determined by counting the pulse before and during stimulation. These changes were very slight as a rule. Of 131 stimuli in the hypothalamus that resulted in marked rises in the blood pressure, 37 had no effect on the pulse rate, 16 caused a slight decrease in rate, 40 caused an increase of from 6 to 12 beats per minute and only 38 produced an increase of more than 12 beats per minute. However, since the pulse rate before stimulation amounted to about 240 per minute, none of the increases obtained are of any great consequence.

Decreases in the pulse rate did not regularly go hand in hand with falls in the blood pressure. Of 42 stimuli which caused falls in the blood pressure of from 10 to 20 mm., 28 had no effect on the pulse rate, 6 resulted in decreases of from 6 to 12 per minute and 8 produced decreases in the pulse rate of more than 12 per minute. Only 6 of 63 stimuli yielding slight falls in the blood pressure effected decreases in the pulse rate exceeding 12 per minute.

The very slight effect of stimulation of the brain on the rate of the heart in our experiments is a rather surprising finding, which will be discussed later.

COMMENT

Rise in Blood Pressure.—It has been possible to trace the response of marked elevations of the blood pressure from the rostral end of the diencephalon without interruption as far caudally as a plane through the inferior colliculi dorsally and the middle of the pons ventrally.

No stimulation was attempted caudal to the inferior colliculi, but there can be little doubt that the pressor pathway descends beyond this point. The reactive zone is well localized throughout, as has been demonstrated in the previous paragraphs, and is confined in the diencephalon to the lateral part of the hypothalamus and the region surrounding the fornix with possible crossings in the supra-optic commissures and in the supramamillary commissure. At the level of the caudal end of the mamillary bodies the pathway seems to divide. One part passes sharply dorsally by way of the periventricular fibers to run caudally through the central gray matter; the other goes directly backward from the hypothalamus into the tegmentum.

The reactive region in the hypothalamus seems to contain a center for raising the blood pressure. In our experiments we were able to trace a pressor mechanism directly caudally from the hypothalamus, while stimulation rostral to this region was ineffective. Karplus and Kreidl [11] proved that the hypothalamus contains a center for pupillary dilatation by stimulating it after degeneration of corticofugal fibers. Although such evidence is not available with respect to the response of the blood pressure, the region of the hypothalamus from which pupillary dilatation can be elicited [12] coincides so closely with the reactive region for elevation of the blood pressure that there is little reason to doubt that vasomotor impulses also originate in the hypothalamus. No evidence was obtained from our extensive explorations that any pressor fibers enter the hypothalamus from the cerebral cortex, thalamus or corpus striatum.

It must be emphasized that with the method employed it is not possible to settle the question of whether the cells or the fibers of the reactive area are essential for the response. Therefore, many of the structures which have been described as being very responsive may not themselves be concerned. Certain nuclei may be responsive only because of pressor fibers passing through them or because of a spread of current to reactive points very close by. Stimulation of certain myelinated fibers may be effective only because of excitation of adjacent cells or of finer unmyelinated fibers that cannot be seen in Weil preparations. However, fiber tracts which are very reactive in their course through the hypothalamus and unresponsive elsewhere can be definitely eliminated, while other bundles almost certainly play a rôle in the pressor effect.

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11. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: II. Ein Sympathicuszentrum im Zwischenhirn, Arch. f. d. ges. Physiol. **135**:401, 1910.

12. Ranson, S. W., and Magoun, H. W.: Respiratory and Pupillary Reactions Induced by Electrical Stimulation of the Hypothalamus, Arch. Neurol. & Psychiat. **29**:1179 (June) 1933.

Our experience in different investigations on stimulation of the brain has been that stimulation of cells is as a rule ineffective and that it is only when a bundle of functionally similar fibers is stimulated that vigorous responses can be elicited. This is explained by the punctate stimulus produced by the bipolar electrodes employed. This, along with the scarcity of the cells in the lateral hypothalamic area, has suggested the possibility that this area is responsive because of the stimulation of fibers and that those fibers arise in the nuclei of the medial hypothalamus. One of the structures which we have shown to be definitely reactive is the subfornical component of the medial bundle of the forebrain (Krieg [8]). It is also quite likely that the periventricular fibers carry hypothalamic pressor impulses into the central gray matter of the mesencephalon and that the hypothalamicotegmental fibers conduct at least part of the pressor impulses that reach the tegmentum. We cannot, of course, determine conclusively whether the axons of hypothalamic cells go all the way down the brain stem or whether there are a number of synapses on the way. The present opinion in regard to the conduction of visceral impulses in the brain stem favors conduction by chains of short neurons.

Other investigators [13] have also attempted to localize a vasomotor center in this region. Beattie [1b] claimed that only the posterior part of the hypothalamus yields a rise in the blood pressure on stimulation, a finding which we have been unable to confirm. Karpus and Kreidl [5] showed that stimulation of the hypothalamus produced a rise in the blood pressure, while the region of the infundibulum was unresponsive.

According to Sachs,[14] who employed the Horsley-Clarke instrument to orient his electrodes, stimulation of certain parts of the thalamus, such as the nucleus reuniens and the nucleus lateralis ventralis, results in a rise in the blood pressure. In our experiments the thalamus was unresponsive. The only reactive region of the diencephalon dorsal to the hypothalamus was near the midline along the course of the periventricular fibers at the level of the mamillary bodies. An examination of illustrations 8, 11 and 12 in Sachs' paper would suggest the possibility that the structure which he labels nucleus reuniens contains the periventricular fibers just mentioned and that the structure which he labels nucleus lateralis ventralis includes the area of transition from the hypothalamus to the mesencephalic tegmentum, which area we have also found to be reactive. It is interesting to note that Sachs observed

13. (*a*) Jaeger, M., and van Bogaert, A.: Hypertension hypothalamique expérimentale; sa nature, Compt. Rend. Soc. de biol. **118**:546, 1935. (*b*) Wang, G., and Richter, C. P.: Action Current from Pad of Cat's Foot Produced by Stimulation of Tuber Cinereum, Chinese J. Physiol. **2**:279, 1928.

14. Sachs, E.: On the Relation of the Optic Thalamus to Respiration, Circulation, Temperature and the Spleen, J. Exper. Med. **14**:408, 1911.

marked rises in the blood pressure during stimulation of the central gray matter surrounding the aqueduct.

Stimulation of the caudate and lenticular nuclei rarely caused any significant changes in the blood pressure. These nuclei were unresponsive in our own experiments and in those of Sachs.[14] Spiegel and Takano [15] could not elicit pressor responses from the corpus striatum after degeneration of the corticofugal fibers in the internal capsule. Although Schüller [16] produced rises in the blood pressure by stimulation of the caudate nucleus in the curarized dog, he could obtain no definite effect by stimulation in noncurarized animals.

Various workers [17] have reported that the rises in the blood pressure which can be elicited on stimulation of the internal capsule are abolished by degeneration of the corticofugal motor fibers. Whether this finding is due to the fact that the changes in the blood pressure obtained are secondary to movements or due to degeneration of cortical vasomotor fibers has not been settled. Schüller [16] was able to elicit rises in the blood pressure by stimulation of the internal capsule in three curarized dogs. According to Hunsicker and Spiegel,[18] stimulation of the cortex of the frontal lobe after curarization causes vasoconstriction much more rarely than vasodilatation. Our own results show that a significant rise in the blood pressure is an unusual result of stimulation of the internal capsule and basis pedunculi. We are inclined to favor the view that the occasional rises in the blood pressure observed were secondary to the somatic movements that result from stimulation.

The pressor response from the hypothalamus is independent of movements of skeletal muscles and changes in the respiratory rhythm. In our experiments the rise in the blood pressure almost always preceded the onset of the somatic movement. Marked responses of the blood pressure have often been observed unaccompanied by any movement, while many stimuli which resulted in vigorous somatic movements had no effect on the blood pressure. The last statement is especially clear from the results of stimulation of the internal capsule. It is interesting to note that spitting may occur along with either a rise or a fall in the blood pressure, depending on the location of the point stimulated. Furthermore, in two experiments on curarized cats (fig. 5 *A*) we were able to demonstrate conclusively that marked rises in the

15. Spiegel, E. A., and Takano, K.: Zur Analyse der vom Streifenhügel erhaltenen Reizwirkungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **118**:429, 1929.

16. Schüller, A.: Reizversuche am Nucleus caudatus des Hundes, Arch. f. d. ges. Physiol. **91**:447, 1902.

17. Friedberg, C. K.: Zur Frage der Identität der corticalen somatischen und vegetativen Zentren nach Reizversuch an der degenerierten inneren Kapsel, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:50, 1931. Spiegel and Takano.[15]

18. Hunsicker, W. C., and Spiegel, E. A.: Conduction of Cortical Impulses to the Autonomic Nervous System, Proc. Soc. Exper. Biol. & Med. **31**:974, 1934.

blood pressure can occur unaccompanied by even the slightest movement of the striated muscles. The experiments with curare also prove that the effect on blood pressure is not secondary to a change in respiration, which is also indicated by the fact that marked rises in the blood pressure may occur together with either an increase or a decrease in the respiratory rhythm.

Quite recently, Leiter and Grinker,[9] after stimulating the hypothalamus in a number of cats, came to the conclusion that there is no vasomotor center in the hypothalamus and that any rises in the blood pressure which result from stimulation are secondary to somatic movements or respiratory disturbances. Our own experiments furnish no evidence for such a view. We have obtained some of the most marked rises in blood pressure that we have ever seen during stimulation in the completely paralyzed animal. Karplus and Kreidl [19] repeatedly observed hypertension during stimulation of the hypothalamus in the curarized cat. In an attempt to settle this question, Jaeger and van Bogaert [13a] demonstrated without the use of drugs that the response of the blood pressure to stimulation of the hypothalamus is independent of somatic movements and changes in respiration.

The very short latent period obtained by ourselves and by Karplus and Kreidl [5] as well as the fact that these investigators could evoke rises in the blood pressure by stimulation of the hypothalamus after removal of the adrenal glands and the hypophysis indicates that the vasomotor mechanism acts essentially through nervous channels. Epinephrine may, however, play a rôle, since Houssay and Molinelli [20] and Beattie, Brow and Long [21] have demonstrated that stimulation of the hypothalamus leads to a secretion of epinephrine. Bilateral removal of the sympathetic chains from the neck to and including the greater splanchnic nerves completely abolishes the response of the blood pressure on stimulation of the hypothalamus, according to Jaeger and van Bogaert.[13a] They showed that after removal of all of the cervical and thoracic sympathetic chains, with the exception of one greater splanchnic nerve, stimulation of the hypothalamus results in an attenuated response of the blood pressure. After injection of ergotamine tartrate, stimulation of the hypothalamus had no effect on the blood pressure.

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19. Karplus, J. P., and Kreidl, A.: Gehirn und Sympathicus: IV. Arch. f. d. ges. Physiol. **171**:192, 1918. Karplus & Kriedl.[5]

20. Houssay, B. A., and Molinelli, E. A.: Centre adrénalino-sécréteur hypothalamique, Compt. rend. Soc. de biol. **93**:1454, 1925.

21. Beattie, J.; Brow, F. R., and Long, C. N. H.: Hypothalamus and Sympathetic Nervous System: I. The Dependence of Extrasystolic Arrhythmia of the Heart Produced by Chloroform upon the Integrity of the Sympathetic System, in The Vegetative Nervous System, A. Research Nerv. & Ment. Dis., Proc. **9**: 249, 1928.

As we have seen, stimulation of the hypothalamus gives rise to only very slight changes in the pulse rate. There was, however, a tendency to an increase in rate, though the magnitude of the changes was very slight—of 131 marked rises in the blood pressure elicited by stimulation of the hypothalamus, 78 were accompanied by some increase in the pulse rate. This suggests the possibility that the stimulus tends to cause an acceleration of the heart rate, which is largely prevented by the reflex inhibition of the heart through the vagus nerves brought about by the precipitate rise in the blood pressure. Further support for this view is furnished by the fact that many times immediately following cessation of an effective stimulus the pulse became much slower and deeper, indicating that during stimulation there was a sympathetic influence which suppressed this vagus effect (fig. 1). Jaeger and van Bogaert [22] obtained an acceleration of the heart rate by stimulation of the hypothalamus, followed sometimes by a strong bradycardia lasting from four to six seconds. Sachs [14] observed that marked rises in the blood pressure elicited from the caudal part of the diencephalon and the central gray matter were not accompanied by changes in the pulse rate.

Since somatic muscular activity is not responsible for the pressor responses and since neither a secretion of epinephrine nor an increase in pulse rate is a factor of importance, we may conclude that the system which we have described is a true vasomotor mechanism, acting largely through nervous channels to constrict the blood vessels.

The hypothalamus not only contains a vasomotor mechanism but is concerned in the dilatation of the pupils,[23] the secretion of epinephrine,[20] the secretion of sweat,[18] the inhibition of gastro-intestinal peristalsis [24] and the erection of hair [24] and possibly in the acceleration of the heart rate.[21] All of these functions are mediated by the sympathetic nervous system, so that the suggestion has been made that a general sympathetic center is located in this region. The hypothesis has also been put forward [25] that this sympathetic center discharges during strong emotion.

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22. Jaeger, M., and van Bogaert, A.: Régulation de la tension arterielle et hypothalamus, Compt. rend. Soc. de biol. **118**:544, 1935.

23. Karplus and Kreidl.[18] Ranson and Magoun.[12]

24. Kabat, H.; Anson, B. J.; Magoun, H. W., and Ranson, S. W.: Stimulation of the Hypothalamus with Special Reference to Its Effect on Gastro-Intestinal Motility, Am. J. Physiol. **112**:214, 1935.

25. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, with Special Reference to the Sympathetic Nervous System, Am. J. Physiol. **84**:490, 1928. Ranson, S. W.: The Hypothalamus: Its Significance for Visceral Innervation and Emotional Expression, Proc. Coll. Physicians, Philadelphia **2**:222, 1934. Kabat; Anson; Magoun and Ranson.[24]

Fall in Blood Pressure.—The falls in the blood pressure obtained by stimulation were not as marked as the rises, nor did they occur as consistently. Nevertheless, we were able to trace a continuous depressor pathway from the most rostral level stimulated to the rostral end of the diencephalon. This pathway is apparently cortical in origin. A decrease in amplitude often associated with a decrease in the rate of respiration, sometimes amounting to complete inhibition, was obtained on stimulation of most of those parts of the telencephalon which yielded falls in the blood pressure: the gyrus genualis and the white matter adjacent to it (fig. 3 *A*), the genu of the corpus callosum and the structures ventral to it (fig. 3 *C*), the anterior commissure not far from the midline, the septum and the preoptic region (figs. 3 *D* and 4 *A*). It is interesting that the depressor path that we have traced by stimulation (figs. 3 *A* to 4 *A*) coincides almost exactly with the so-called tractus neocorticoseptalis described by Wallenberg.[26] After destruction of the frontal pole, he traced degeneration by the Marchi method through the middle of the ventral half of the white center of the hemisphere in a circumscribed bundle, along the medial edge of the frontal pole of the lateral ventricle, in the ventral part of the genu of the corpus callosum and then through the septum pellucidum. In the diencephalon the points that yielded falls in the blood pressure on stimulation were mostly localized in the thalamus, but we were unable to trace an uninterrupted depressor pathway. In the mesencephalon no definite pathway was evident, and effective points were mostly localized in the lateral part of the tegmentum and in the habenulopeduncular tract. The fall in the blood pressure is probably not dependent on changes in the respiration or somatic movements, since it has been observed along with either an increase or a decrease in the rate and depth of respiration and was only rarely accompanied by a movement of the skeletal muscles.

Our failure to trace the depressor pathway caudally beyond the level of the anterior commissure may indicate that at this level it enters the hypothalamus and its constituent fibers become mingled with those of the pressor mechanism. Under these conditions electrical stimulation of the hypothalamus might be expected to produce only rises in the blood pressure due to the dominant action of the vasoconstrictor mechanism. The depressor pathway may be interrupted by a number of synapses. One such synaptic station is perhaps located in the septum and the preoptic area.

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26. Wallenberg, A.: Bemerkenswerte Endstätten der Grosshirnfaserung bei Säugern (Verlauf und Endigung der Faserung aus der Neurinde des Frontalpols beim Meerschweinchen, insbesondere ihre Beziehung zum Septum pellucidum), Jahrb. f. Psychiat. u. Neurol. **51**:295, 1934.

Very few investigators have observed falls in the blood pressure during stimulation of the brain. Spiegel and Takano [15] obtained occasional falls in the blood pressure from the head of the caudate nucleus which could no longer be elicited after degeneration of the fibers from the motor cortex. Schüller [16] also evoked some falls in the blood pressure on stimulation of the caudate nucleus. Sachs [14] sometimes saw a fall in the blood pressure during stimulation of the anterior nucleus of the thalamus. Hunsicker and Spiegel [18] noted that, after curarization, stimulation of the cortex of the frontal lobe caused vasodilatation much more frequently than vasoconstriction and that these reactions were somewhat better preserved after section of the pyramidal tracts than after destruction of the tegmentum and the central gray matter.

We have found that changes in the pulse rate very rarely accompanied the falls in the blood pressure. When such a change did occur, however, it was always in the direction of a slowing of the heart rate (fig. 2). Either slight tachycardia or slight bradycardia may result from stimulation of the cortex of the frontal lobe.[18] According to Kennard,[27] stimulation of the premotor cortex in monkeys leads to slowing of the heart rate.

Beattie [1b] has localized a parasympathetic center in the anterior and tuberal portions of the hypothalamus. We have found no evidence for such a localization. The only parasympathetic response consistently produced by stimulation of the diencephalon is contraction of the bladder,[28] and this could be traced forward to a center in the preoptic area and septum pellucidum.

The fact that the response of the bladder can be traced to the preoptic area and septum and that this region also yields falls in the blood pressure suggested the possibility that a parasympathetic center might be located in this region. However, this hypothesis has been abandoned for very good reasons. The depressor pathway can be traced almost to the frontal pole and is probably of cortical origin. Stimulation of the preoptic area and septum pellucidum never causes constriction of the pupils or increased motility of the gastro-intestinal tract,[24] nor does it result in defecation, erection of the penis, salivation or lacrimation, all of which are parasympathetic responses. Furthermore, in contrast to the sympathetic system, which tends to discharge as a whole, the various portions of the parasympathetic system usually act independently of one another.

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27. Kennard, M.: Vasomotor Representation in the Cerebral Cortex, Science **79**:348, 1934.

28. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Reaction of the Bladder to Stimulation of Points in the Forebrain and Midbrain, J. Comp. Neurol., to be published. Ranson; Kabat and Magoun.[2b] Kabat; Anson; Magoun and Ranson.[24]

CONCLUSIONS

The response of elevation of the blood pressure has been traced by stimulation from the rostral end of the diencephalon as far caudally as a plane through the inferior colliculi dorsally and the middle of the pons ventrally. In the diencephalon the responsive points were localized in the lateral hypothalamic area and medial bundle of the forebrain, the perifornical nucleus and the H_1 field of Forel, with possible crossings in the supra-optic commissures and the supramamillary commissure. From the hypothalamus part of the pathway passes sharply dorsally in the periventricular fibers and goes caudally through the central gray matter, while another part goes directly caudally through the tegmentum.

Stimulation of points in the telencephalon, thalamus, internal capsule and basis pedunculi, corpus striatum and superior and inferior colliculi failed to effect significant rises in the blood pressure.

Only very slight and sometimes no acceleration of the heart rate accompanied the rises in the blood pressure.

Evidence is presented that the rises in the blood pressure are independent of somatic movements or changes in the respiratory rhythm.

Depressor responses were traced without interruption from just behind the frontal pole of the hemisphere as far caudally as the rostral end of the diencephalon, beyond which a continuous pathway could not be followed. The reactive region, which appears to be a corticifugal pathway, includes the ventromedial portion of the white center of the frontal lobe, the band of fibers medial to the rostral end of the lateral ventricle, the septum pellucidum and the preoptic area. In the diencephalon, depressor points were localized in certain parts of the thalamus. In the mesencephalon, the lateral part of the tegmentum yielded some falls in the blood pressure.

These results are discussed in their relation to the hypotheses that sympathetic and parasympathetic centers are present in the forebrain

VOLUME OF BLOOD IN NORMAL SUBJECTS AND IN PATIENTS WITH SCHIZOPHRENIA

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The theory that the malfunction in schizophrenia is due in greater or less degree to decreased oxygenation in the tissues, especially those of the nervous system, has frequently been postulated. That the basal rate of oxygen consumption rate in patients with schizophrenia is decreased is now generally accepted. This failure of the body tissues of the schizophrenic patient to utilize oxygen to the same degree as those of the normal subject might be due either to a deficiency arising in the cells themselves or to a breakdown in the mechanism for delivering oxygen. In the first case, the malfunction might be caused by a lack of oxidative catalysts or a disarrangement of the specific ability of the cells to absorb the oxygen which is supplied to them. In the second case, a number of factors might play a part. The unit concentration of hemoglobin might be decreased through either a deficiency in erythrocytes or a lowering of the amount of hemoglobin in each cell. The amount of blood delivered per minute might be decreased. This question is now under investigation, and the results will be given in a later paper. The amount of oxygen carried by the cells per unit volume of blood might be decreased by changes in the oxygen-combining power of the hemoglobin. The velocity of the blood flow might be altered, and, finally, the total volume of blood in the body might be decreased. Each factor requires special consideration, as changes in one might be compensated by opposing changes in another. Thus, if the total volume of blood were diminished, this could be offset by an increase in the velocity. In this investigation we are concerned with the concentration of hemoglobin and the total volume of blood.

MATERIAL

To this end determinations of the blood volume were made on a group of eighty-seven male patients with schizophrenia and on twenty-nine normal men, who were connected with the hospital as physicians, employees or students. Three

From the Memorial Foundation for Neuro-Endocrine Research and the Research Service of the Worcester State Hospital.

determinations were made on the patients at intervals of three months, during the course of the "seven month study."[1] However, only the determinations made during the last period and a single subsequent determination on twenty-five additional patients are utilized for comparison with the values for normal subjects.

It should be noted that the normal subjects, so far as could be ascertained, were all healthy and were not suffering from any acute infection at the time of the study. The need for careful studies on the various physiologic functions of normal persons has been repeatedly brought to our attention during the course of our investigations on schizophrenia. It is unfortunate that much work in the past on control subjects has been performed on patients in hospitals, who cannot be considered entirely normal. It is hoped that the findings reported in this paper will help to overcome this deficiency.

METHOD

The volume of blood was determined by the use of congo red, as recommended by Rowntree, Brown and Roth,[2] after a sample of blood for use as a control was taken from the median basilic vein of one arm. An amount of a 1.5 per cent solution of congo red equivalent in the number of cubic centimeters to one fourth of the body weight expressed in kilograms was injected into the same vein. The patient then exercised mildly by placing one foot on a stool 18 inches (45.72 cm.) high and stepping up and down ten times with the other foot. The second sample of blood was taken after three minutes and before six minutes had elapsed. Five cubic centimeters of blood from the control and from the experimental sample, respectively, were placed in two graduated centrifuge tubes containing 1 cc. of a 1.6 per cent solution of sodium oxalate. The samples of blood were drawn in the morning while the subjects, who were fasting, were lying down. In order to measure the amount of dye injected, the syringes were filled from an accurate volumetric buret. The sterile solution of dye, warmed to a temperature of about 40 C., was placed in the buret, and the syringe was attached by a short length of rubber tubing, fitted with an adapter. Dye was sucked into the syringe, and then the plunger was pressed home to eject all the dye and bubbles of air from the apparatus. The level of the dye in the buret was then read, and the dye was drawn into the syringe until the predetermined volume was obtained, as indicated on the buret. A slight amount of suction was used, so that the space between the plunger and the barrel was always completely filled. The stopcock on the buret was then turned, and the syringe was removed for the injection. Care was taken to avoid any loss of dye by its escape from the vein into the surrounding tissue. In any case in which such a loss was noted by careful inspection of the arm, the results were not used. Every precaution was taken to prevent hemolysis by using absolutely dry syringes and needles and by transferring the blood from the syringe to the centrifuge tubes carefully and without force. The centrifuge tubes were capped with heavy finger cots and centrifugated for thirty minutes at 3,000 revolutions per minute. At first the tubes were centrifugated after reading for ten minutes longer to insure the maximum packing of the red corpuscles, but as it was found that no change resulted in the readings, the second centrifugation was not continued.

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1. Hoskins, R. G., et al.: A Cooperative Research in Schizophrenia, Arch. Neurol. & Psychiat. **30**:388 (Aug.) 1933.

2. Rowntree, L. G.; Brown, G. E., and Roth, Grace M.: The Volume of the Blood and Plasma, Philadelphia, W. B. Saunders Company, 1929.

The centrifuge tubes were calibrated by comparison with an accurate buret, and it was found that readings could be made with a maximum error of 1 per cent.

The solution of congo red used was prepared by dissolving the dye in distilled water, passing the solution through a Berkefeld filter and subsequently autoclaving it at a pressure of 15 pounds for thirty minutes. No untoward results were noted by the use of this solution in over two hundred injections.

The standard was prepared by diluting 1 cc. of the same solution of dye to a volume of 200 cc. in a volumetric flask. Two cubic centimeters of this standard was added to 2 cc. of the plasma obtained before injecting the dye and 4 cc. of physiologic solution of sodium chloride. The unknown solution was prepared by mixing 2 cc. of the plasma containing the dye with 6 cc. of the saline solution. The solutions were compared in a colorimeter, and the volumes of both plasma and whole blood were calculated.

TABLE 1.—*Constants of Distribution of Blood and Plasma Volumes for Eighty-Seven Patients and Twenty-Nine Normal Subjects Used as Controls Irrespective of Weight* *

	No. of Subjects	Minimum	Maximum	Mean and σ	S.D. and σ	C.V., Percentage
Blood volume, cc.						
Patients	87	3,170	6,757	4,837 ± 75	703 ± 53	14.5
Controls	29	4,147	6,683	5,258 ± 135	716 ± 96	13.6
Plasma volume, cc.						
Patients	87	1,684	3,505	2,594 ± 44	409 ± 31	15.8
Controls	29	2,235	3,830	2,853 ± 79	417 ± 56	14.6
Blood volume, cc. per Kg. of body weight						
Patients	87	55.2	99.0	79.3 ± 0.89	8.33 ± 0.63	10.5
Controls	29	69.0	97.6	81.4 ± 1.38	7.30 ± 0.98	9.0
Plasma volume, cc. per Kg. of body weight						
Patients	87	29.3	57.5	42.6 ± 0.62	5.82 ± 0.44	13.7
Controls	29	36.3	52.7	44.1 ± 0.78	4.13 ± 0.55	9.4
Blood volume, cc. per sq. m. of body surface						
Patients	87	1,865	3,969	2,824 ± 33	307 ± 23	10.9
Controls	29	2,560	3,559	3,007 ± 49	257 ± 34	8.5
Plasma volume, cc. per sq. m. of body surface						
Patients	87	991	2,050	1,509 ± 20	190 ± 14	12.6
Controls	29	1,016	1,968	1,610 ± 35	187 ± 25	11.6
Red cells, hematocrit reading						
Patients	87	31	57	46.1 ± 0.42	3.91 ± 0.30	8.5
Controls	29	40	58	47.2 ± 0.77	4.07 ± 0.54	8.6

* In this table and in tables 3 and 4, σ indicates the standard error; S.D., the standard deviation, and C.V., the coefficient of variation.

RESULTS

The results of this investigation are given in table 1 for all the patients and for the normal subjects used as controls. In this table all the patients are considered, irrespective of weight. It will be noted that there is no significant difference between the volume of blood per kilogram of body weight for the patients and that for the normal subjects, the mean value for the former group being 79.3 cc. and that for the latter, 81.4 cc. The plasma volumes also show no significant difference, the mean value for the patients being 42.6 cc. per kilogram and that for the normal subjects, 44.1 cc. However, if the volumes are considered in relation to the surface area, it is found that the mean value of 2,824 cc. per square meter of body surface for the patients is sig-

nificantly lower than that of 3,007 cc. for the control subjects, as the difference of 183 cc. is more than three times the standard error. With regard to the plasma volumes, calculated on the basis of the number of cubic centimeters per square meter of body surface, the difference between the mean value of 1,509 cc. for the patients and that of 1,610 cc. for the normal control subjects is on the borderline of significance.

The percentage of red cells as determined by the hematocrit is essentially the same for the two groups, the values for the patients being 46.1 per cent and that for the normal subjects, 47.2 per cent.

The comparison of values for all the patients with those for all the normal subjects, irrespective of weight, is, however, open to criticism on the ground that it has been shown that the blood volume, expressed in cubic centimeters per kilogram of body weight, is greater for groups of persons who are underweight than for those of standard weight. In this respect the values are weighted in favor of the patients, as in their group 55 per cent of the subjects were underweight, 39 per cent of standard weight, and 6 per cent overweight, while in the group control 17 per cent were underweight, 69 per cent of standard weight and 14 per cent overweight.

However, when the volumes are considered on the basis of weight, the number of normal subjects who were underweight is only five and hence is not large enough to warrant conclusions. The majority of the patients are included in this group. The difference between the values for the patients and those for the control group is 6.2 cc. per kilogram, while that between the values for the groups as a whole is only 2.1 cc. per kilogram. It is probable, therefore, that if a larger group of underweight normal subjects were included a significant difference might be found. This appears reasonable in view of the fact that a significant difference appears when the volumes are compared on the basis of surface area, a relation which Rowntree has shown to be subject to less variation than the amount of blood per kilogram of body weight in the various groups based on weight.

No significant difference was found for any of the variables presented in the constants for the subjects of standard weight in either the group of patients or that of control subjects.

The groups of overweight subjects consisted of only five patients and four normal subjects; so data from these groups do not warrant separate consideration.

COMMENT

The values for the volume of blood obtained for the normal control subjects in our series are approximately 10 per cent lower than those given by Rowntree, Brown and Roth,[2] as recorded in table 2. The values which we obtained, however, agree well with those

of Silbert, Kornzweig and Friedlander,[3] who found for a mixed group of twenty-two hospital patients free from vascular disease a total blood volume of 82.7 cc. per kilogram of body weight, a plasma volume of 44.7 cc. and a hematocrit value for red cells of 45 per cent. Hodskins, Guthrie and Naurison,[4] for a control group of forty-two subjects, 65 per cent of which were men, obtained somewhat lower values: 77 cc. per kilogram for the blood volume and 46.3 cc. for the plasma volume. Their value of 39.7 per cent for red cells determined by hematocrit readings was, however, even lower than that of 42 per cent given by Rowntree. Our value for the percentage of red cells in the blood as obtained by the use of graduated centrifuge tubes for twenty-nine normal control subjects was 47.2. This is in close agreement with the value of 48.3 per cent found in another study on sedimentation rates obtained for fifty normal persons by Freeman,[5]

TABLE 2.—*Mean Values for Normal Subjects of Different Body Builds*[2]

						Blood		Plasma		Hemoglobin			
Subjects	Number	Sex	Weight, Kg.	Height, Cm.	Body Surface, Sq. M.	Cc. per Kg. of Body Weight	Gm. per Sq. M. of Body Surface	Cc. per Kg. of Body Weight	Cc. per Sq. M. of Body Surface	Gm. per 100 Cc. of Blood	Gm. per Kg. of Body Weight	Gm. per Sq. M. of Body Surface	Cells, Percentage Hematocrit Reading
Underweight.....	12	M	59.6	169.0	1.68	92.0	3,265	53.5	1,900	16.8	14.9	547	41
Of standard weight	29	M	69.5	171.2	1.82	89.1	3,410	51.0	1,958	16.7	15.0	541	42
Overweight.....	8	M	77.6	170.0	1.89	81.8	3,347	46.7	1,923	16.3	13.3	532	42
All groups.....	49	M	68.1	170.0	1.80	88.6	3,365	51.0	1,938	16.4	14.7	541	42

using heparinized blood in sedimentation tubes. The low hematocrit values of Hodskins may have been due in part at least to the effect of using a concentrated solution of oxalate—0.1 cc. of a 20 per cent solution of potassium oxalate—which has been shown by Whipple to cause shrinkage of the red cells.

The hematocrit value for the percentage of red cells found in Freeman's study of the sedimentation rate for forty-seven of the same patients used in this investigation was 45.4 per cent, and this, too, corresponds with our value of 46.1 per cent.

3. Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Thrombo-Angiitis Obliterans (Buerger): IV. Reduction of Blood Volume, Arch. Int. Med. **45**:948 (June) 1930.

4. Hodskins, M. B.; Guthrie, R. H., and Naurison, J. Z.: Study in Blood Volumes of Epileptics, Am. J. Psychiat. **11**:623, 1931.

5. Freeman, H.: Sedimentation Rate of the Blood in Schizophrenics, Arch. Neurol. & Psychiat. **30**:1298 (Dec.) 1933.

The volumes which we obtained are also in agreement with those of Rusznak,[6] who for eleven normal subjects found a mean value of 82.6 cc. per kilogram for blood and of 44.5 cc. for plasma.

In table 3 are given the constants for the distributions pertaining to age, weight and surface area for the patients according to weight groups and for the normal subjects. It will be seen that the two groups are well matched as regards age, height and surface area but that there is a preponderance of underweight subjects in the group of patients. The constants of distribution for hemoglobin determined by the various methods of estimation for the patients and the control subjects are given in table 4. The hemoglobin was estimated by the Haden hemo-

TABLE 3.—*Constants of Distribution Pertaining to Age, Weight and Surface Area for Patients with Schizophrenia and for Normal Subjects During the Second Period and One Additional Month of Study*

Variable	Group of Subjects	No. of Subjects	Minimum	Maximum	Mean and σ	S.D. and σ	C.V., Percentage
Age, years	Underweight	48	18.	45	30.5 ± 1.07	7.42 ± 0.76	24.3
	Of standard weight	34	18	44	28.9 ± 1.16	6.78 ± 0.82	23.5
	Overweight	5	29	36	31.0		
	All patients	87	18	45	29.9 ± 0.75	7.02 ± 0.53	23.5
	All normal subjects	29	20	43	27.8 ± 1.00	5.02 ± 0.71	18.1
Height, cm.	Underweight	48	142.2	186.6	171.3 ± 1.28	8.89 ± 0.91	5.2
	Of standard weight	34	157.0	185.4	170.2 ± 0.98	5.74 ± 0.70	3.4
	Overweight	5	162.6	189.5	173.1		
	All patients	87	142.2	189.5	171.0 ± 0.84	7.85 ± 0.60	4.6
	All normal subjects	29	155.0	180.3	169.3 ± 1.26	6.88 ± 0.89	3.9
Body weight, kg.	Underweight	48	43.8	76.4	56.6 ± 0.91	6.30 ± 0.64	11.1
	Of standard weight	34	56.8	75.0	64.8 ± 0.92	5.39 ± 0.65	8.3
	Overweight	5	67.8	100.4	83.6		
	All patients	87	43.8	100.4	61.4 ± 0.99	9.21 ± 0.70	15.0
	All normal subjects	29	54.0	84.4	64.7 ± 1.46	7.70 ± 1.03	11.9
Body area, square meters	Underweight	48	1.32	1.98	1.66 ± 0.019	0.129 ± 0.013	7.8
	Of standard weight	34	1.57	2.00	1.75 ± 0.017	0.102 ± 0.012	5.8
	Overweight	5	1.75	2.26	1.98		
	All patients	87	1.32	2.26	1.72 ± 0.016	0.145 ± 0.011	8.4
	All normal subjects	29	1.56	2.03	1.74 ± 0.022	0.117 ± 0.016	6.7

globinometer, and the results for both the patients and the control subjects agree well with the values of Haden, who gave 15.6 Gm. of hemoglobin per hundred cubic centimeters of blood as the normal content. For the control subjects in our series the hemoglobin content was 15 Gm. per hundred cubic centimeters of blood, and for the patients, 15.2 Gm. That the hemoglobin content for the patients was almost identical with that for the normal group is of interest in view of the fact that the erythrocyte count has been found to be somewhat diminished. There was no significant difference between the amount of hemoglobin for the patients and that for the control subjects, on the basis

6. Rusznak, S.: Untersuchungen zur Frage der Gesamtblutmenge des Menschen unter normalen und pathologischen Verhältnissen, Deutsches Arch. f. klin. Med. **157**:186, 1927.

either of the total content or of the number of grams per hundred cubic centimeters of blood, per kilogram of body weight or per square meter of body surface.

Because of the large number of observations possible, it seemed desirable to calculate the coefficients of correlation for the relationships of the blood and plasma volumes and the various body measurements, such as height, weight and surface area. No significant differences

TABLE 4.—*Constants of Distribution Pertaining to Hemoglobin for Patients and Normal Subjects*

Group of Subjects	No. of Subjects	Minimum	Maximum	Mean and σ	S.D. and σ	C.V., Percentage
Total Gm. of hemoglobin						
Patients						
Underweight	47	507	974	694.20 ± 15.42	104.57 ± 10.90	15.06
Of standard weight	33	568	1,006	772.73 ± 17.94	101.52 ± 12.69	13.14
Overweight	4	778	1,023	862.5		
All patients	84	507	1,023	729.61 ± 12.51	113.95 ± 88.47	15.62
Controls						
Of standard weight	14	535	976	734.2 ± 32.6	117.6 ± 23.1	16.00
All normal subjects	22	535	993	767.8 ± 26.4	121.0 ± 18.7	15.80
Gm. per 100 cc. of blood						
Patients						
Underweight	47	13.5	16.5	15.01 ± 0.11	0.73 ± 0.08	4.86
Of standard weight	33	12.5	16.5	15.40 ± 0.19	1.07 ± 0.13	6.95
Overweight	4	15.0	15.5	15.3		
All patients	84	12.5	17.5	15.2 ± 0.10	0.88 ± 0.07	5.82
Controls						
Of standard weight	14	12	16	14.8 ± 0.29	1.06 ± 0.21	7.20
All normal subjects	22	12	16	15.0 ± 0.20	0.93 ± 0.14	6.20
Gm. per Kg. of body weight						
Patients						
Underweight	47	8.8	15.4	12.2 ± 0.19	1.38 ± 0.14	10.44
Of standard weight	33	9.5	15.9	11.96 ± 0.29	1.62 ± 0.28	13.42
Overweight	4	9.6	11.5	10.4		
All patients	84	8.8	15.9	12.00 ± 0.16	1.46 ± 0.11	12.17
Controls						
Of standard weight	14	8.9	13.9	11.8 ± 0.37	1.35 ± 0.26	11.40
All normal subjects	22	8.9	14.9	12.1 ± 0.31	1.41 ± 0.22	11.70
Gm. per square meter of body surface						
Patients						
Underweight	47	298	512	421.35 ± 6.76	45.83 ± 4.78	10.88
Of standard weight	33	336	565	440.99 ± 9.43	53.38 ± 6.67	12.11
Overweight	4	415	453	434.2		
All patients	84	298	565	425.01 ± 5.44	49.57 ± 3.85	11.66
Controls						
Of standard weight	14	330	498	431.4 ± 13.5	48.6 ± 9.5	11.30
All normal subjects	22	330	506	443.2 ± 10.0	46.0 ± 7.1	10.40

were obtained between the relationships of these various factors for normal subjects and those for the patients, possibly because the number of the control subjects was insufficient to reveal differences that might be evident in a larger series. Likewise, the coefficients of correlation for the two groups were not significantly different from those reported by Rowntree and Brown, and they are for that reason not enumerated in this paper.

In order to study the relationship of body weight and blood volume in still more detail, we also attacked the problem on the basis of indi-

vidual changes appearing during the interval from the second to the third period of study. We have therefore determined the coefficients of correlation for the relationship of body weight in the third period and that in the second and likewise the coefficients for the blood and plasma volumes for these two periods. The coefficient of correlation for body weight for the two periods is high, a value of 0.95 ± 0.01 being obtained, but the coefficient for blood volumes is much lower, with a value of only 0.70 ± 0.07. The coefficient for plasma volume is even lower, being 0.61 ± 0.08.

These values indicate that while the body weight remains fairly constant the blood volume and the plasma volume show considerable fluctuation. It is not surprising, then, to find that the relationship of the blood volume per kilogram of body weight for the third period and that for the second period shows only a slight correlation, as indicated by its coefficient of 0.29 ± 0.12. This value is significantly lower than the coefficient for the relationship of blood volume and body weight for different persons. It would appear that the coefficient of correlation between blood volume and body weight for different persons is higher than that for the same person at different times. This may be due in part at least to a disturbance in water metabolism which permits fluctuations in the blood volume even though the body weight remains fairly constant. Evidence suggestive of disturbed water metabolism in these patients is seen in the high daily output of urine, which is approximately twice that for subjects in the normal group.

There appears to be an indication that the blood volume for the patients is lower than that for the normal group, particularly when measured on the basis of surface area. This difference would not in itself be sufficient to account for the deficiency in the consumption of oxygen observed in the patients, but when considered with the fact that this smaller volume also circulates at a slower rate, as shown by Freeman,[7] the total effect might well be of importance. That the decrease in oxygen made available to the tissues is the cause of the lowering of the basal rate of oxygen consumption seems somewhat improbable; rather it is the decreased demand of the tissues for oxygen that results in the slowing of the circulation. The findings are in harmony with the idea that suboxidation of the tissue may occur.

SUMMARY

The volume of whole blood and that of plasma were determined by the congo red method of Rowntree for eighty-seven male patients with schizophrenia and for twenty-nine normal men.

7. Freeman, H.: The Arm to Carotid Circulation Time in Normal and Schizophrenic Subjects, Psychiatric Quart. **8:** 290, 1934.

The total volume of blood was 79.3 cc. per kilogram of body weight for the patients and 81.4 cc. for the normal subjects. The total volume of plasma was 42.6 cc for the patients and 44.1 cc. for the control subjects. There is no significant difference between these values.

On the basis of the number of cubic centimeters of blood per square meter of body surface the blood volume for the control group had a significantly higher value—3,007 cc. as compared with 2,824 cc. for the patients. The plasma volume per square meter of body surface was also significantly higher for the normal subjects, with a value of 1,610 cc., than for the patients, with a value of 1,509 cc.

The volume of red cells as determined by the hematocrit was essentially the same, that for the patients being 46.1 per cent and that for the control group, 47.2 per cent.

The volume of blood was found to be correlated with various body measurements, the coefficients for the patients being 0.48 for height, 0.73 for body weight and 0.74 for surface area. Similar values for plasma were 0.48, 0.59 and 0.62. The coefficients for the control group were somewhat higher though not significantly different, being 0.69 for height, 0.77 for weight, and 0.85 for surface area. The coefficients for the plasma were 0.71, 0.77 and 0.87, respectively.

The concentration of hemoglobin was found to be 15.2 Gm. per hundred cubic centimeters of blood for the patients and 15 Gm. for the control subjects.

CONCLUSION

There is a decrease in the total circulating volume of whole blood in patients with schizophrenia considered as a group, when measured on the basis of surface area.

TUMORS OF THE CORPUS CALLOSUM

A PATHOLOGIC AND CLINICAL STUDY

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This study is the result of pathologic and clinical analyses of thirty-eight cases of tumor that involved the corpus callosum to some degree. These cases were included in a series of three hundred and fourteen cases of microscopically verified tumor of the frontal lobe which have previously been reported (Voris, Kernohan and Adson [1] and Voris, Moersch and Adson [2]). We thought it worth while to make a separate report of the results of study of this group of cases because of the opportunity thus afforded for comparing the findings with those previously reported for the larger series.

According to Ironside and Guttmacher,[3] the earliest verified cases of tumor of the corpus callosum on record are those described by Plater in 1614 and by Wepfer in 1675. Gradually a large number of reports of such cases have appeared in the literature, together with some complete studies of the anatomy, physiology and pathology of the corpus callosum. Of the latter, the papers of Lévy-Valensi [4] and of Ironside and Guttmacher are among the best. The largest individual series which we have found has been that of Armitage and Meagher; [5] this series consisted of twelve cases from Cushing's clinic.

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1. Voris, H. C.; Kernohan, J. W., and Adson, A. W.: Tumors of the Frontal Lobe: An Anatomic and Pathologic Study, Arch. Neurol. & Psychiat. **34**:605 (Sept.) 1935.

2. Voris, H. C.; Moersch, F. P., and Adson, A. W.: Tumors of the Frontal Lobe: Clinical Observations in a Series Verified Microscopically, J. A. M. A. **104**:93 (Jan. 12) 1935.

3. Ironside, R., and Guttmacher, M.: Corpus Callosum and Its Tumors, Brain **52**:442 (Dec.) 1929.

4. Lévy-Valensi, J.: Le corps calleux (étude anatomique, physiologique, et clinique), Thèse de Paris, 1910; Physiologie du corps calleux, Presse méd. **19**:72 (Jan. 28) 1911.

5. Armitage, George, and Meagher, Richard: Gliomas of the Corpus Callosum, Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:454, 1933.

The clinical picture and consequently the diagnosis of these lesions have always been somewhat obscure and confused, and there has been considerable difficulty in correlating the clinical picture with the results of experimental physiology. In 1890, Mott and Schaefer [6] reported that they had obtained bilateral movements of the head, trunk and limbs of monkeys on stimulation of the corpus callosum with the faradic current, insulated electrodes being used. Lévy-Valensi, however, was able to obtain movements only of the face, neck and trunk with similar stimulation of the corpus callosum; with strong currents he was able to obtain movements of the limbs, but under these circumstances he could not eliminate diffusion of the current to the motor centers in the adjacent hemispheres. After section of the corpus callosum of both monkeys and dogs he observed no abnormalities except apathy and some loss of acquired habits.

Kennard and Watts,[7] in recent experiments, sectioned the corpus callosum of monkeys, but they were not able to produce motor weakness or reflex grasping in previously normal animals, nor were they able to produce any effect on previously produced syndromes of the motor or premotor areas. Inertia and slowness in initiating purposeful movements were observed after section of the corpus callosum. This finding apparently corresponds to the motor apraxia so often described clinically in cases of lesions of the corpus callosum.

ANATOMIC AND PATHOLOGIC GROUPING

We have divided our cases into two groups from an anatomic standpoint: The first group consists of seventeen cases in which the tumor originated primarily in the corpus callosum and invaded one or both frontal lobes secondarily; the second group consists of twenty-one cases in which the tumor originated in one of the frontal lobes and invaded the corpus callosum secondarily. The clinical observations for these two groups will be presented side by side in some of the tables to afford opportunity for comparison.

The tumors were all gliomas and were classified as follows: oligodendroblastoma in two cases, spongioblastoma multiforme in twenty-six cases, polar spongioblastoma in one case, astroblastoma in two cases, ependymoma in one case, astrocytoma in four cases, oligodendroglioma in one case and gangliocytoma in one case. In Armitage and Meagher's series of twelve cases of glioma of the corpus callosum, eight of the tumors were classified as spongioblastoma multiforme and four as fibril-

6. Mott, F. W., and Schaefer, E. A.: On Movements Resulting from Faradic Excitation of the Corpus Callosum in Monkeys, Brain **13**:174, 1890.

7. Kennard, Margaret A., and Watts, J. W.: The Effect of Section of the Corpus Callosum on the Motor Performance of Monkeys, J. Nerv. & Ment. Dis. **79**:159 (Feb.) 1934.

lary astrocytoma. The proportion of tumors of the spongioblastoma multiforme type is approximately the same, 70 and 75 per cent, respectively, for the two series.

CLINICAL ANALYSIS

Table 1 gives the incidence of the tumors according to the decades of life and the sex of the patients. These tumors are predominately of adult life, occurring in more than 75 per cent of cases during the fourth, fifth and sixth decades. The male sex predominated over the female in the ratio of a little more than 2:1. This is approximately the same ratio as was seen in the previously reported series of cases of glioma involving the frontal lobes.

The initial complaint in cases of intracranial tumor is always a matter of interest, as it may often be the only symptom for a considerable period of time. In these cases headache was the most common initial complaint, occurring in fourteen of the thirty-eight cases. Next in frequency was some type of convulsive seizure, which occurred as the initial complaint in ten cases; grand mal was the

TABLE 1.—*Incidence by Decades and Sex of Thirty-Eight Tumors of the Corpus Callosum*

Decades, Years	Males	Females
1 to 10	..	1
11 to 20	..	1
21 to 30	4	2
31 to 40	8	5
41 to 50	8	1
51 to 60	6	1
61 to 70	..	1
Total	26	12

most frequent type (seven cases), whereas jacksonian attacks occurred in one case and petit mal in two cases. Some type of mental change was the initial complaint in eight cases. In the remaining six cases general debility was the initial complaint in two, dizziness in two, paresthesia in one and insomnia in one. There was no essential difference in the initial symptoms from the tumors that were primary in the corpus callosum and those that involved the corpus callosum secondarily, except that convulsive attacks of some sort occurred as the initial symptom in six cases, or 35 per cent, of the former group, and in only four cases, or 19 per cent, of the latter group.

When the various complaints from which each patient suffered are considered, headache again leads in frequency, being present in all but five of the thirty-eight cases (table 2). Some type of mental change was the next most frequent complaint, being present in thirty-one cases. It should be pointed out that these are cases in which some type of mental change was complained of by the patient or was mentioned by those accompanying him at the time when he first came to the clinic. The various types of mental change seen will be discussed more in detail in connection with the findings on examination of the patients in the series.

Nausea and vomiting were next in frequency, being present in twenty-seven cases. As in the previously reported series of cases of tumor of the frontal lobe, they are considerably outranked in frequency by headache (as earlier pointed out

by Frazier and Gardner[8]), with which they are usually bracketed in discussion of the symptoms of tumors of the brain. Projectile vomiting was rare, and when it was present it had usually occurred on only a few occasions and had been associated with more frequent vomiting of the usual type.

Convulsive attacks of some sort were present in twenty-four cases. Grand mal occurred in fourteen cases, or 37 per cent of the total number. This is almost equal to its incidence in the cases of tumor of the frontal lobe (39 per cent). Jacksonian attacks of focal convulsions and petit mal were less frequent, the former being seen in six cases and the latter in four.

Visual disturbance of some sort was present in about a third of the cases, and weakness or paralysis of one side of the body in ten cases. The latter finding, as might be expected, was seen much more frequently in the group of cases in which the tumor originated in the frontal lobe and invaded the corpus callosum secondarily. It occurred in seven cases in this group and in only three cases in which the tumor had its primary origin in the corpus callosum.

TABLE 2.—*Various Complaints in Thirty-Eight Cases of Tumor of the Corpus Callosum*

Complaint	Cases	Tumor of the Corpus Callosum	
		Primary	Secondary
Headache	33	14	19
Mental change	31	15	16
Nausea and vomiting	27	11	16
Convulsive attacks	24	10	14
Grand mal	14	7	7
Jacksonian fits	6	2	4
Petit mal	4	1	3
Visual disturbances	13	5	8
Hemiparesis	10	3	7
Total	38	17	21

The most frequent finding at examination, exclusive of some type of mental change, was some degree of choking of the optic disks, from 1 diopter to a maximum of 7 to 8 diopters (table 3). It occurred in twenty-four cases, or 63 per cent of the group, which corresponds almost exactly to the percentage of its occurrence in the series of cases of tumor of the frontal lobe.

It is interesting that weakness or paralysis of the facial muscles of central origin occurred in half of the cases in the series and more than twice as frequently as weakness or paralysis of the extremities. Sachs[9] and others have emphasized contralateral central facial weakness as an important diagnostic sign of tumor of the frontal lobe. We did not find it so in our group of cases of tumor of the frontal lobe, and here we find confirmatory evidence that this is not a positive diagnostic sign of such tumors.

8. Frazier, C. H., and Gardner, W. J.: The Mechanism and Symptoms of Increased Intracranial Pressure Due to Encapsulated and Infiltrating Tumors of the Cerebral Hemispheres, in The Intracranial Pressure in Health and Disease, Association for Research in Nervous and Mental Diseases, Baltimore, Williams & Wilkins Company, 1929, vol. 8, p. 386.

9. Sachs, Ernest: Lesions of the Frontal Lobe, Arch. Neurol. & Psychiat. **24**:735 (Oct.) 1930.

The heading "cerebellar signs" includes the findings of ataxia and incoordination or adiadokokinesis of the extremities. One or more of these signs of cerebellar involvement were present in half of the cases. This incidence is considerably greater than the frequency of these findings in the cases of tumor of the frontal lobe, which was 32 per cent, and appears to be somewhat confirmatory of Hare's [10] conclusions that median line tumors are more likely to produce symptoms referable to the cerebellum. We have discussed in previous reports the probable anatomic explanation of the cerebellar phenomena seen in cases of tumor in the frontal lobe.

Reflex disturbances, including increase in tendon reflexes, decrease in cutaneous reflexes or the presence of pathologic reflexes, such as Hoffmann's, Babinski's or Rossolimo's sign, were encountered in eighteen cases. Sphincteric disturbances were next in frequency, occurring in fifteen cases, or almost 40 per cent of the group. The relatively frequent occurrence of this symptom corresponds to the frequency of some degree of stupor or coma, as will be seen in the discussion of the mental phenomena.

TABLE 3.—*Findings at Examination in Thirty-Eight Cases of Tumor of the Corpus Callosum*

Findings at Examination	Cases	Tumor of the Corpus Callosum	
		Primary	Secondary
Choked disks	24	11	13
Paresis (seventh nerve)	19	6	13
Signs of cerebellar involvement	19	7	12
Reflex disturbances	18	5	13
Sphincteric disturbances	15	7	8
Hemiparesis	8	2	6
Aphasia	8	5	3
Field defects	7	3	4
External ocular palsies	7	2	5
Special signs	6	3	3
Nystagmus	4	4	0
Sensory disturbances	2	1	1
Total	38	17	21

Weakness or paralysis of the extremities of one side was present in eight cases, in all but two of which the tumor originated in one frontal lobe and invaded the corpus callosum secondarily. Some degree of disturbance of speech was present in an equal number of cases, in five of which the primary origin of the tumor was in the corpus callosum.

Some form of perimetric field defect was present in seven cases. In no case was this finding of localizing value. External ocular palsies, usually of the external rectus muscle but occasionally of muscles innervated by the oculomotor or trochlear nerve, were also present in seven cases.

Under the heading special signs we have included such findings as reflex or so-called forced grasping, apraxia, deviation of the head or eyes and "perseveration" or retardation of motor movements. One or more of these signs were present in six cases, only 16 per cent of the series. Since Wilson [11] and others have

10. Hare, C. C.: The Frequency and Significance of Cerebellar Symptoms in Tumors of the Frontal Lobes, Bull. Neurol. Inst. New York **1**:532, 1931.

11. Wilson, S. A. K.: A Contribution to the Study of Apraxia, with a Review of the Literature, Brain **31**:164, 1908.

emphasized the importance of motor apraxia as a diagnostic sign of lesions of the corpus callosum, its infrequent occurrence in our cases is of interest.

Nystagmus of some type was encountered in four cases, in all of which the tumor had its primary origin in the corpus callosum. Objective sensory disturbances of one side of the body were seen in two cases.

As previously stated, some type of mental change was the most frequent finding at examination. In addition to the thirty-one patients with a complaint of mental change, four more on examination presented objective evidence of some mental abnormality; thus, thirty-five, or 92 per cent of the total, exhibited some evidence of mental abnormality. This is considerably higher than the figure (70 per cent) that was met with in the previously reported series of cases of tumor of the frontal lobe. All of the patients with tumor primary in the corpus callosum had some type of mental abnormality. This corresponds to Armitage and Meagher's figures and to those for the group collected from the literature by Giannelli,[12] as their patients all gave evidence of some type of mental change.

TABLE 4.—*Mental Changes in Thirty-Eight Cases of Tumor of the Corpus Callosum*

Mental Changes	Cases	Tumor of the Corpus Callosum	
		Primary	Secondary
Loss of memory	26	13	13
Indifference to environment	24	12	12
Change in personality or character	23	11	12
Drowsiness, stuporous or comatose state	23	11	12
Disorientation (time and place)	13	8	5
Witzelsucht, euphoria, puerility	10	5	5
Delirium states	5	4	1
Depression states	4	2	2
Total	38	17	21

As in previous reports, it is reiterated that our records have been made primarily from the standpoint of clinical neurology and not from that of psychiatry. On the one hand, this insures that the figures given represent well marked phenomena, but, on the other, it may account in part for the lower percentage of imponderable phenomena, such as disorders of humor or character. With these reservations, the different types of mental symptoms encountered are recorded in table 4.

Loss of memory, especially for recent events, was the most frequent mental symptom and occurred in twenty-six cases, or almost three fourths of the cases in which the patient had some type of mental abnormality. Occurring with almost equal frequency were the phenomena of indifference to environment, some type of change in personality or character and some degree of somnolence, ranging from simple drowsiness to profound coma.

Disorientation in time or space was encountered in thirteen cases, and some type of change in character or emotion, such as Witzelsucht, euphoria, moria, puerility, etc., was encountered in ten cases. Delirium states were present at some time during the course of the illness in five cases, in four of which the tumor was primary in the corpus callosum. Depression states were seen in four cases.

12. Giannelli, A.: Gli effetti diretti ed indiretti dei neoplasmi encefalici sulle funzioni mentali, Policlinico (sez. med.) **4**:301 (July 15) 1897.

It is obvious that, as far as this group of cases of tumor involving the corpus callosum is concerned, some type of abnormal mental phenomenon is a very common finding and the type seen is more often some form of depression of the mental faculties and might be described under the term hypomania.

COMMENT

The diagnosis of tumor of the corpus callosum has not often been made during life. Since the advent of ventriculography it has occasionally been made with the aid of this procedure. Even at operation these tumors, because of this situation, are not often verified.

It is evident that as far as the cases in this series are concerned the outstanding clinical features are early signs of increased intracranial pressure associated with marked mental changes. Motor manifestations, including convulsions, unilateral or bilateral paralysis, reflex disturbances and apraxia, are often present. Signs of involvement of the cerebellum are frequently seen and may at times cause confusion in the diagnosis, but when they are associated with convulsions or with signs of involvement of the pyramidal tract they should not lead to error. Perhaps the most difficult problem is to distinguish tumors of the corpus callosum from lesions of the frontal lobe, as comparison of the findings in this group of cases with those previously reported for the entire series of cases of tumors of the frontal lobe readily demonstrates. According to Lévy-Valensi, the anterior part of the corpus callosum is most frequently involved by tumor. In his review he has presented the figures for the situation of the tumor in seventy-four cases from the literature, where this fact was given. The entire corpus callosum was involved in nineteen cases, the genu in twenty-eight, the splenium in nineteen and the body alone in eight. In none of the reports that we have reviewed has the involvement of adjacent structures been described adequately.

As previously stated, in the group here presented, the genu, or genu and body, or in a few cases the entire corpus callosum, was involved, and in all cases there was some involvement of the frontal lobes with additional involvement in a few cases of the parietal lobe. In reviewing a large number of cases of supratentorial tumor in connection with this and previously reported studies, we found only two cases in which the tumor was grossly confined to the corpus callosum. This factor of subcortical involvement of the frontal lobes probably accounts in part for the similarity of findings for the two groups, but we are convinced that the chief difficulties in the diagnosis of these tumors will usually be in distinguishing them from frontal, and occasionally from cerebellar, lesions. Ventriculography will probably often have to be called on to establish definitely the diagnosis, and perhaps it should be used more often, as this particular group of tumors is not amenable to surgical measures except from the standpoint of palliative decompression.

SUMMARY

The pathologic and clinical findings in thirty-eight cases of tumor involving the corpus callosum are presented. All the growths were gliomas, 70 per cent being classified as spongioblastoma or glioblastoma multiforme. The outstanding clinical features are the marked mental changes and early signs of increased intracranial pressure which are often associated with various motor phenomena, including "cerebellar signs."

DISCUSSION

DR. RICHARD B. RICHTER: I have always believed that a knowledge of tables of findings of the kind presented is rather futile in the diagnosis of certain individual problems. I wish to ask how often it was necessary to resort to ventriculography as a means of diagnosis in differentiating these tumors, especially in differentiating lesions of the frontal fossa from those of the posterior fossa.

DR. LEWIS J. POLLOCK: While perhaps not entirely germane to tumors of the corpus callosum, but included as part of the symptomatology, there are the signs of involvement of the cerebellum. I think that the clinical neurologist should take note of the need for a clear definition of dysfunction of the cerebellum. In certain cases symptoms and signs have been observed when parts of the cerebellum have been destroyed. These have consisted of various signs, adiadokokinesis, for example. This is not necessarily a sign of disease of the cerebellum. Similarly, I have no doubt that disease of parts other than the cerebellum may produce defects in cocontraction and distribution of tone of the reciprocal muscles.

The point I raise is, why should one state that in cases of supratentorial lesions there are signs referable to the cerebellum. When hemiparesis occurred in only 9 of the cases, as contrasted with the number of cases in which there were signs of involvement of the cerebellum, is it not rather a challenge to determine what defects other than those in the cerebellum produce these disturbances in motor function, rather than to attempt to explain them on some hypothetic anatomic basis? Destruction of the cerebellum as a whole does not produce signs analogous with those described. In decerebrate animals Davis and I showed that the cerebellum acted rather as a whole in inhibiting muscle tone. I think that before they can be content to accept the view that signs and symptoms of involvement of the cerebellum occur in cases of supratentorial lesions clinicians should find a method of determining the function of the cerebellum.

DR. HAROLD C. VORIS: In answer to Dr. Richter, so far as I can determine from the records a diagnosis was not made in any of these cases before surgical measures were instituted. The presence of a deep-seated tumor was often detected during removal of biopsy material with a trocar, but so far as I know from the records there was no diagnosis of tumor of the corpus callosum made before operation.

EFFECT OF EXTRACT OF ADRENAL CORTEX ON EXPERIMENTAL NEUROSIS IN SHEEP

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It has long been known that definite and enduring nervous disturbances can be produced experimentally in certain mammals. Abnormal states of the nervous system were observed in the dog a number of years ago by Pavlov and his associates [1] during the course of experiments on the conditioned reflex. When the conditions of the experiments were such that an animal was called on to solve a problem beyond its capacity, e. g., to distinguish between two closely similar conditioned stimuli, the dog receiving food with one and not with the other, it often happened that the behavior of the animal exhibited a profound change. The formerly friendly and quiet animal became extremely fractious and disturbed, and in this condition it was unable to solve even the simplest problem.

In 1927 Liddell and Bayne [2] observed this derangement of behavior in a sheep during conditioning experiments in which the animal was called on to react to a definite time interval by a movement of the left foreleg in anticipation of an electric shock. The sheep was unable to make the required adjustment, and as the routine of training was continued its behavior exhibited a sudden change. The animal no longer stood on the experimental table with its habitual quiet but showed great restlessness. During the intervals between tests fre-

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1. Pavlov, I. P.: Conditioned Reflexes, translated by G. V. Anrep, New York, Oxford University Press, 1927.

2. Liddell, H. S., and Bayne, T. L.: The Development of Experimental Neurasthenia in the Sheep During the Formation of Difficult Conditioned Reflexes, Am. J. Physiol. **81**:494, 1927.

quent jerking movements of the foreleg to which the electrodes were attached were observed. The sheep finally became extremely agitated, even when being handled in preparation for each day's experiment, and all attempts to work with it had to be abandoned.

In 1929 this type of disturbance was again observed, and in 1931 it appeared twice in the course of experiments on conditioned motor reflexes with sheep. The characteristics of the "experimental neurosis" were nearly identical in all our animals and are described fully in another paper.[3] Briefly, they manifest themselves in the alteration from extreme docility characteristic of the "normal" trained animal to great nervousness, reluctance to enter the experimental room, signs of agitation during the experiment and inability to solve problems which were formerly handled with ease.

The "experimental neurosis" in the sheep seemed to be permanent. In the case of one animal it had persisted for five years, and although the sheep became quieter after complete rest for a year, the nervous symptoms reappeared and attained their former severity within a short time after the experiments were resumed.

We had not attempted any curative procedures, except to give the animals a complete rest from the experiments for a considerable period, but that nature could possibly be aided in the matter had been suggested by Pavlov, who observed improvement in his "neurotic" dogs as the result of the administration of bromides.

It occurred to one of us that extract of the adrenal cortex might have a beneficial influence on this disturbance in the sheep, for previous studies (Hartman, Brownell and Lockwood[4]) had shown that the extract has a pronounced effect on the nervous and muscular systems generally. Thus, in cases of Addison's disease[5] extract of adrenal cortex was found to relieve the symptoms of extreme muscular weakness and marked nervousness, in addition to affording relief from the other signs of the disorder. Effects of the substance could be detected in normal human subjects as well.[6] Mental fatigue was often diminished; sleep was improved, and a sense of well-being was experienced, which developed in some cases even to the point of euphoria.

3. Anderson, O. D., and Liddell, H. S.: Observations on Experimental Neurosis in Sheep, Arch. Neurol. & Psychiat. **34**:330 (Aug.) 1935.

4. Hartman, F. A.; Brownell, K. A., and Lockwood, J. E.: Studies Indicating the Function of Cortin, Endocrinology **16**:521, 1932.

5. Hartman, F. A.; Thorn, G. W.; Lockie, L. M.; Greene, C. W., and Bowen, B. D.: Treatment of Addison's Disease with an Extract of Suprarenal Cortex (Cortin), J. A. M. A. **98**:788 (March 5) 1932.

6. Hartman, F. A., and Thorn, G. W.: The Effect of Cortin in Asthenia, Proc. Soc. Exper. Biol. & Med. **29**:48, 1931.

Hartman and Lockwood [7] have shown that the reflexes of adrenalectomized rats are a great deal more easily fatigued than those of normal rats. The administration of extract of adrenal cortex increased the resistance to fatigue sixfold. Recently, Hartman, Beck and Thorn [8] have demonstrated that the extract has a definite beneficial effect on the nervous and mental symptoms of disorders unrelated to Addison's disease (functional and organic diseases of the nervous system). Marked improvement was noticed not only in the motor functions of the patients (diminution in fatigability and increase in strength) but in their mental outlook. States of profound depression and general irritability were replaced in varying degree by cheerfulness and calmness.

In the light of these findings we designed experiments to study systematically the progress of the abnormal nervous condition in the sheep during the repeated administration of adrenal cortex extract, including observations on the behavior of normal as well as of "neurotic" animals.

METHOD

Method.—The extract was administered to the animals daily for a period of about a week. The daily dose was given in two subcutaneous injections, one in the morning and one in the afternoon. Each injection was followed, after a predetermined interval, by a test of the animal's behavior. Thus, there were two test periods each day. Each period lasted from one-half to one hour. Control tests were made on each animal during a period of two days just preceding the critical tests.

For the sake of clearness a typical day's procedure may be cited. The animal, having been given an injection at 9 a. m., while in the barn, is allowed to remain there with the other animals till 12, when it is taken to the experimental room and placed in position on the table. The electrode is attached to the left foreleg, and to the same limb is fastened a string leading from a recording lever in the adjoining instrument room, where any movement of the leg is traced on the smoked paper of a kymograph. When these preparations are completed, the experimenter leaves the room and allows the sheep a few minutes in which to become adjusted to the surroundings. The buzzer is then sounded for ten seconds, and this is followed by the application of a brief series of induction shocks (one-fifth second) to the leg. The animal is carefully observed through a window, and notes concerning its behavior are made. The speed of the kymograph is then reduced so that the behavior can be recorded throughout a period of seven minutes, thus giving a compact record. At the end of seven minutes the buzzer is again sounded for exactly ten seconds, followed by the shock, after which the behavior is again recorded and observed continuously for seven minutes. The stimulation

7. Hartman, F. A., and Lockwood, J. E.: The Effect of Cortin on the Nervous System in Adrenal Insufficiency, Proc. Soc. Exper. Biol. & Med. **29**:141, 1931.

8. Hartman, F. A.; Beck, G. M., and Thorn, G. W.: Improvement in Nervous and Mental States Under Cortin Therapy, J. Nerv. & Ment. Dis. **77**:1, 1933.

is then given again, and so on to the end of the test period. The straps are removed, and the animal is returned to the barn. It then receives a second injection. After another three hour period the sheep is returned to the laboratory for the testing of conditioned reflexes, where the same test is repeated.

Our standard test was four stimulations (the sound of the buzzer followed by the electric shock), and each stimulation was separated by an interval of seven minutes from the one following it.

In these tests behavior could be studied quantitatively as well as qualitatively. In addition to descriptive notes of the behavior observed in the barn or in the laboratory, we had at hand a means of estimating quantitatively the magnitude or vigor of the conditioned reflex during the standard ten second period of stimulation. During that time the limb to which the electrode was attached would in a phlegmatic animal be flexed three or four times, the foot being raised each time from 6 to 9 inches (15 to 23 cm.) from the platform. This type of reaction we had previously termed "weak." In other and more lively sheep the limb would be flexed eight or ten times in the same period, the foot being raised each time from 10 to 15 inches (25 to 38 cm.). This type of reaction we had referred to as "strong." We sought a means of stating these descriptions in numerical terms, and for this purpose we have used with good results for four years a modification of Fick's work accumulator.[9] The device is so arranged that it registers in millimeters the reduced height of each flexion of the limb and gives the total value for the magnitude of successive movements occurring during the standard time. The "weak" reaction may thus register only 100 mm., while the "strong" may have a magnitude of 300 mm. or more. In addition to this quantification we can estimate with considerable accuracy the degree of nervousness of the disturbed sheep at a particular time by counting the number of the spontaneous or "nervous" movements of the leg recorded during the constant rest interval between stimuli. We have thus been enabled to follow the progress of the neurosis over a long period, and this has been of great value in the present experiment.

The work was carried out during the spring and summer of 1932, during which four series of experiments were performed. Four sheep (designated 7, 11, 8 and A) were employed in the experiments. Of these four animals sheep 7 and 11 were normal; sheep 8 and A were neurotic. The previous conditioning of animals 8 and A and the circumstances responsible for the development of the "neurosis" in these sheep are described in a previous paper.[3]

In the present experiments the sound of the buzzer served as the only conditioned stimulus for sheep 7, 11 and 8. The time interval between stimuli varied for sheep 7 from three to seven minutes, but it was always seven minutes for sheep 11 and 8. For sheep A both the buzzer and the metronome were used. This animal had formerly differentiated between 120 beats of the metronome per minute (always followed by shock) and 92 beats per minute (never followed by shock). The ability to make the easiest differentiation, that between 120 and 50 beats of the metronome, was tested repeatedly to see whether or not it would be regained by sheep A during the administration of adrenal cortical extract. The interval between conditioned stimulations was five minutes in the case of this animal.

OBSERVATIONS

SERIES 1.—In a preliminary investigation of this kind the first experiment was naturally exploratory. Its aim was not only to determine the nature of the effect

9. Liddell, H. S.: The Conditioned Reflex, in Moss, F. A.: Comparative Psychology, New York, Prentice-Hall, Inc., 1934, chap. 9.

of the extract but to attempt to find out the time required for the extract to act, i. e., the time, expressed in hours, necessary for a single injection to produce its maximal effect.

In this series the extract was administered to all four animals. Sheep 7, 8 and A were each given 5 cc. daily (1 cc. contained the product of 30 Gm. of adrenal cortex) in two subcutaneous injections of 2.5 cc. each, while sheep 11 was given the same amount each day in a single injection. All the animals were tested twice a day except sheep 11, which was tested only once. The extract was administered for four days to sheep 7 and 11, the normal animals, and for five days to sheep 8 and A, the neurotic animals.

In an attempt to determine the time necessary for the cortical extract to exert its effect, the animals were tested each day at a different time after the injection. Thus, each test was made two hours after the injection on the first day, three hours afterward on the second, four hours afterward on the third, five hours afterward on the fourth and for sheep 8 and A four hours afterward on the fifth. For sheep 7 (normal) and sheep 8 and A (neurotic) an injection of 2.5 cc. of physiologic solution of sodium chloride was substituted as a control before the first test period of the second day, and the second test of that day was preceded by an injection of 5 cc. of extract of adrenal cortex.

Results.—The behavior of all the animals was altered in a striking manner during the administration of the extract. In the laboratory the conditioned reflex greatly increased in magnitude and vigor in both the normal and the neurotic animals. In the reaction each movement of the "conditioned" limb remained precise; i. e., although the reflex was extremely vigorous, it did not consist of diffuse and violent struggling involving the movement of all four limbs but centered on the limb to which the electrode was attached. Each flexion was in most cases maximal, the foot being raised to the greatest possible height from the platform, and the number of such movements occurring during the ten second period of stimulation was markedly increased. In previous experiments it was found that the movements began usually three or four seconds after the start of stimulation, but under the present circumstances the reaction began usually within one or two seconds.

In the interval between stimuli the behavior of the normal sheep remained unchanged, and its conduct outside the laboratory seemed not to be affected in any way. The behavior of the disturbed animals, on the other hand, at such times underwent a definite alteration. Although their conditioned reactions were greatly increased in magnitude, the signs of nervousness became at the same time much less evident, not only in the laboratory but outside. A graphic record of the behavior of neurotic sheep 8 while extract of adrenal cortex was being administered is shown in figure 1 *C*. The maximal flexions of the limb during two applications of the buzzer followed by shock and the relative quiet of the animal in the interval between tests are apparent. The behavior pictured in this tracing and that recorded for the same animal before the extract was administered (fig. 1 *B*) may be compared.

The two nervous animals remained perfectly quiet on the laboratory table on some occasions when no stimuli were presented, and a considerable improvement was noticed in their reactions when they were being brought to the laboratory. At such times each animal trotted willingly to the room, climbed quickly on the table and at once ate the food offered. But although they showed every evidence of being much calmer than at any time since the development of the neurosis, they could never be handled as easily as the normal trained sheep. They seemed always somewhat wary of us and carefully watched our every movement.

With neurotic sheep 8 it had been noticed just prior to this experiment that a light touch of the finger on the shaved skin of the "conditioned" limb when the animal was in the laboratory would almost always evoke a defensive movement of the leg. This was, however, very slight and was sometimes merely a kind of tremor or a rapid series of twitches of the muscles of the limbs and shoulders, which continued for a few seconds after the finger was removed. During the administration of the extract of adrenal cortex, however, the reaction was rarely seen. Tests for this effect were made just before each experimental period, while the sheep was being prepared. This phenomenon was never observed in the normal sheep, and indeed sheep 8 was the only neurotic animal in which it appeared.

TABLE 1.—*Effect of Repeated Small Doses of Extract of Adrenal Cortex on the Magnitude of the Conditioned Motor Reflex in Normal and in Neurotic Sheep*

	Normal		Neurotic	
	Sheep 7	Sheep 11*	Sheep 8	Sheep A
Average magnitude expressed in mm. of the conditioned reflex during tests of 2 days preceding administration of extract of adrenal cortex (16 stimuli)	**30**	**159**	**238**	**116**
Average magnitude expressed in mm. of the conditioned reflex in each test period during administration of extract of adrenal cortex (4 stimuli in each test)				
First day				
2.5 cc. 2 hours before a.m. test	7	...	273	47
2.5 cc. 2 hours before p.m. test	30	194	465	130
Second day				
2.5 cc. saline solution 3 hours before a.m. test	68	...	275	80
5 cc. 3 hours before p.m. test	68	181	308	125
Third day				
2.5 cc. 4 hours before a.m. test	45	...	437	73
2.5 cc. 4 hours before p.m. test	**87**	**205**	**577**	110
Fourth day				
2.5 cc. 5 hours before a.m. test	57	...	346	214
2.5 cc. 5 hours before p.m. test	61	149	345	**235**
Fifth day				
2.5 cc. 4 hours before a.m. test	...	...	390	131
2.5 cc. 4 hours before p.m. test	...	...	289	152
Sixth day				
A.M. test	...	...	...	...
P.M. test	...	...	228†	...

* Normal sheep 11 was given only one test period a day following a single daily injection of 5 cc. of extract of adrenal cortex. The time elapsing between the injection and the test period was the same as for the other animals in this series.

† The test period was not preceded by injection of extract of adrenal cortex on this day.

Neurotic sheep A showed no evidence while the extract was being given of regaining its former ability to make the easy differentiation between 120 and 50 beats of the metronome per minute. It always reacted vigorously to both positive and negative stimuli with the metronome, as it had always done since the development of the experimental neurosis.

The quantitative results concerned with the magnitude of the conditioned reflex and the number of the spontaneous movements of the leg during the intervals of rest between conditioned stimuli show clearly the same facts. The entire course of the behavior of the animals before and during the injections of extract of adrenal cortex is presented in summary in tables 1 and 2. In table 1, which includes the data obtained for all four sheep, each value represents the average magnitude, expressed in millimeters, of the conditioned reflex responses to the sound of the buzzer and, in the case of neurotic sheep A, similar values for the responses to 120 metronome beats a minute as well. The average magnitudes of

the reactions to 50 beats of the metronome for neurotic sheep A are not included. The average magnitude of the reflexes obtained in the control tests is shown in the upper line of numbers. Each succeeding horizontal line of numbers shows this average for each test period during the administration of the extract of adrenal cortex.

A definite increase in the magnitude of the conditioned reflex can be seen for all the sheep. An increase is evident for neurotic sheep 8 and A and for normal sheep 11 on the afternoon of the first day, although the values for normal sheep 7 and neurotic sheep A show a decrease during the first test. On the morning of the second day the increase failed to appear for neurotic sheep 8 and A when the tests were preceded by a subcutaneous injection of saline solution instead of the extract of adrenal cortex. But the increase in magnitude of the reflex is obvious for all the animals on the afternoon of that day. The greatest increase appeared on the afternoon of the third day for normal sheep 7 and 11 and for neurotic sheep 8, and on the afternoon of the fourth day for neurotic sheep A. The maximum average values are given in bold face type for comparison with those in the standard tests used as controls. The values show a decline on the fourth day for normal sheep 7 and 11 and for neurotic sheep 8, but they are still higher than the average control values for sheep 7 and 8 and slightly lower than the average control value for sheep 11. On the fifth day the magnitude of the conditioned reflex shows a further decline for neurotic sheep 8 and a considerable decline for neurotic sheep A. On the sixth day, when no extract was given, the average magnitude of the reactions for sheep 8 was slightly lower than the standard.

The maximal increase may be seen to be more than 100 per cent for normal sheep 7 and neurotic sheep 8 and A, and for normal sheep 11 it is almost 30 per cent. Although it has been found that the vigor of the conditioned motor reflex varies normally in the sheep from one trial to another, the difference between the average magnitude of the reaction for one day and that for the next is not great, and the greatest average difference observed has never, in our experience, even approached 100 per cent. Individual differences, however, among the animals are to be expected, and it was for this reason that we decided at the outset of this experiment not to attempt to use as controls a group of animals to which no injections were given but to use a period during which no injections were given as a control for a subsequent period of injections in one and the same animal. The significance of individual differences in the investigation of conditioned reflexes has been fully discussed elsewhere.[10]

That the neurotic sheep are quieter in the laboratory after the administration of the extract is begun is indicated by the diminution in the number of spontaneous movements of the leg. This decrease is shown in table 2. For neurotic sheep 8 during the control tests there were on the average 15 movements of the left forelimb in the seven minute interval between conditioned stimuli, and for neurotic sheep A the average was 11 movements during the five minute rest interval (upper line). This is the typical number of spontaneous movements of the foreleg for a corresponding interval observed for these animals over a period of about a year prior to the administration of the extract. The condition had neither improved nor become worse in that time, the animals being given no period of rest from the laboratory routine. The average number of movements during

10. Liddell, H. S.; James, W. T., and Anderson, O. D.: The Comparative Physiology of the Conditioned Motor Reflex (Based on Experiments with the Pig, Dog, Sheep, Goat and Rabbit), Comparative Psychology Monographs, Baltimore, Johns Hopkins Press, 1934, vol. 11, p. 1.

each interval in each of the two daily test periods during the critical period of injections is shown by the values in the succeeding lines. Comparison of these values with the standard values used as controls shows the amount of decrease in restless or spontaneous activity. This decrease can be seen in the results of the first test of the first day for both neurotic animals. The number of movements decreased further on the second day for sheep 8, although injections of the saline solution had been substituted before the first test of that day. In the first test of the third day sheep 8 remained perfectly quiet during all the rest intervals between conditioned stimuli, and in the afternoon of that day sheep A registered an average of only 1 movement for each interval—the greatest diminution. But for both neurotic animals the number increased on the fourth and fifth days,

TABLE 2.—*Effect of Repeated Small Doses of Extract of Adrenal Cortex on the Number of Spontaneous Movements of the Forelimb in Neurotic Sheep During Interval of Rest Between Stimuli* *

	Neurotic	
	Sheep 8	Sheep A
Average number of spontaneous movements per interval during tests of 2 days preceding administration of extract of adrenal cortex (12 intervals)	15	11
Average number of spontaneous movements of limb per interval in each test period during administration of extract of adrenal cortex (3 intervals in each test)		
First day		
2.5 cc. 2 hours before a.m. test	3	4
2.5 cc. 2 hours before p.m. test	5	2
Second day		
2.5 cc. saline 3 hours before a.m. test	1	2
5 cc. 3 hours before p.m. test	1	5
Third day		
2.5 cc. 4 hours before a.m. test	0	4
2.5 cc. 4 hours before p.m. test	2	1
Fourth day		
2.5 cc. 5 hours before a.m. test	2	8
2.5 cc. 5 hours before p.m. test	4	5
Fifth day		
2.5 cc. 4 hours before a.m. test	7	5
2.5 cc. 4 hours before p.m. test	11	4
Sixth day		
A.M. test	...	...
P.M. test	9†	...

* The interval between conditioned stimuli was five minutes in the case of sheep A and seven minutes in that of sheep 8.

† The test period was not preceded by injection of extract of adrenal cortex on this day.

although the movements were not as frequent as in the tests used as controls. For sheep 8 on the sixth day, one day after the administration of the extract had ceased, the number of nervous movements of the foreleg was considerably less than during the period of control tests.

Comparison of the data in the two tables shows that as the conditioned reflex increased in magnitude the number of spontaneous movements of the leg of the neurotic sheep decreased. This relation, however, is true only in general. When it is considered in detail, there are some exceptions. Thus, in the case of neurotic sheep 8, for example, the conditioned reflex reached its maximum average value of 577 mm. on the afternoon of the third day, but the animal was quietest (with no leg movements) on the morning of the third day when the average magnitude of the reading for the reflexes was only 437 mm. Nevertheless, on the whole, the two factors, the magnitude of the conditioned reflex and the number of spontaneous movements of the leg, appear to be inversely related.

From the results just presented it was not clear to us whether the maximal increase in the magnitude of the conditioned reflex and the maximal decrease in the number of nervous movements reached on about the third day were due to the fact that the pause between an injection and a subsequent test of the conditioned reflexes was four hours on that day, i. e., that four hours were required for the substance to produce its maximum effect. We suspected that the effects of the extract were cumulative and persisted from one day to the next, rising to a maximum and then declining under the continued administration of the extract of adrenal cortex.

SERIES 2.—We decided to repeat the first experiments under a somewhat different set of conditions. It occurred to us, of course, that in order to determine whether or not the apparent effects were cumulative it was necessary to employ always the same interval between each injection of the extract and the test for the conditioned reflex, i. e., to rule out altogether the variable time factor employed in the first experiments. We arbitrarily chose an interval of three hours. We also decided to determine whether or not an increased daily dose of the extract would bring about a corresponding augmentation of the previously observed effects, i. e., whether it would result in a greater increase in the magnitude of the conditioned reflex and a more enduring decrease in the number of nervous movements of the leg.

In the experiments about to be described a single animal was used, the neurotic sheep 8. The tests were begun one month after the previous experiments had terminated, during which time the usual signs of nervousness had reappeared to their full extent. Two daily tests, one in the morning and one in the afternoon, as in the first series, were given for a period of eight days. Each test was made three hours after an injection of 7.5 cc. of the extract (15 cc. a day). No substitution of physiologic solution of sodium chloride was made at any time. All other conditions remained the same as in the first experiments.

During the critical period the conditioned reaction was again found to increase in vigor, and on the whole the augmentation was considerably greater than that seen in the first series. This increase was clearly cumulative. On the other hand, the signs of nervousness became, at the same time, more evident instead of less. As the critical tests progressed, the sheep obviously became more restless and disturbed in each interval and finally became more nervous than at any previous time.

Tests were again made regularly to see whether touching the limb with the finger would evoke a defensive reaction, and during this phase of increasing nervousness the phenomenon was always observed. On a few occasions even touching the abdomen was sufficient to evoke a defensive movement of the forelimb.

The animal on all occasions showed great excitement on being brought to the laboratory.

We thought at first that the increase in nervousness might be due to the fact that the animal had been overworked, i. e., that it had been given too many tests within a short period. We had noticed in earlier experiments that the disturbed animals tended to become more excited and restless if tested more often than three or four times a week. Often it had been found necessary to permit them at such times to rest for a number of days, after which they were somewhat quieter. In the present case it was thought advisable, after the experiment had proceeded for five days, to interrupt it for a pause of five days. During the pause no extract of adrenal cortex was administered, and no tests were made.

At the end of the rest period the experiment was resumed. In the tests of the next three days after the administration of extract of adrenal cortex was begun we were again surprised to find that the animal was still excessively nervous, judging both by the frequency of the spontaneous leg movements and by the extreme excitement outside the laboratory.

The observations just described are expressed quantitatively in tables 3 and 4. In table 3 a considerable increase in the magnitude of the reflex can be seen on the first and second days, and in the first test of the third day the maximal average increase is shown, an increase of from 181 to 686 mm. This enhancement of the conditioned reflex is much greater than that which was observed in the

TABLE 3.—*Effect of Repeated Large Doses of Extract of Adrenal Cortex on Magnitude of the Conditioned Motor Reflex in a Neurotic Sheep*

	Sheep 8
Average magnitude in mm. of conditioned motor reflex during tests of 2 days preceding administration of extract of adrenal cortex (16 stimuli)	**181**
Average magnitude in mm. of conditioned motor reflex in each test period during administration of extract of adrenal cortex (4 stimuli in each test)	
First day	
7.5 cc. 3 hours before a.m. test	350
7.5 cc. 3 hours before p.m. test	230
Second day	
7.5 cc. 3 hours before a.m. test	440
7.5 cc. 3 hours before p.m. test	423
Third day	
7.5 cc. 3 hours before a.m. test	**686**
7.5 cc. 3 hours before p.m. test	629
Fourth day	
7.5 cc. 3 hours before a.m. test	436
7.5 cc. 3 hours before p.m. test	303
Fifth day	
7.5 cc. 3 hours before a.m. test	298
7.5 cc. 3 hours before p.m. test	257
A five day pause occurred during which no extract of adrenal cortex was administered and no tests of behavior were made	
Eleventh day	
7.5 cc. 3 hours before a.m. test	77
7.5 cc. 3 hours before p.m. test	238
Twelfth day	
7.5 cc. 3 hours before a.m. test	357
7.5 cc. 3 hours before p.m. test	340
Thirteenth day	
7.5 cc. 3 hours before a.m. test	408
7.5 cc. 3 hours before p.m. test	372

first experiment, the maximal average increase for this sheep being from 238 to 577 mm. The enhancement became less and less evident on the fourth and fifth days, as observed in the experiments with small doses of extract of adrenal cortex. It was still less evident after the five day pause. With the administration of the extract, however, the magnitude of the conditioned response again increased during the last three days of the experiment.

Table 4, showing the number of spontaneous movements of the forelimb, demonstrates chiefly the great increase in nervousness seen during the course of the experiment. A slight decrease in the number of movements of the leg may be seen on the first critical day, but on the ensuing days the restlessness was greatly augmented. The average frequency of the movements was approximately doubled on the fourth and fifth days and on the first day after resumption of the experiment, but this was followed on the last two days by a slight diminution in the

number of movements. However, the number was, on the whole, greater than that in the preliminary control tests.

SERIES 3.—The results thus far obtained might, we thought, be attributable either to the action of extract of adrenal cortex or to that of epinephrine, or to both acting in combination. We were aware that the extract used contained epinephrine in a concentration of 1 : 200,000. The great increase in the amplitude and vigor of the conditioned defensive movements which was observed suggested a possible effect due to epinephrine. This was also suggested by the augmented nervousness seen in sheep 8 when given an increased dosage of extract of adrenal

TABLE 4.—*Effect of Repeated Large Doses of Extract of Adrenal Cortex on the Number of Spontaneous Movements of the Forelimb in a Neurotic Sheep During the Rest Interval Between Stimuli* *

	Sheep 8
Average number of spontaneous movements of limb per interval during tests of 2 days preceding administration of extract of adrenal cortex (12 intervals).....	12
Average number of spontaneous movements of limb per interval in each test period during administration of extract of adrenal cortex (3 intervals in each test)	
First day	
7.5 cc. 3 hours before a.m. test.....	6
7.5 cc. 3 hours before p.m. test.....	5
Second day	
7.5 cc. 3 hours before a.m. test.....	6
7.5 cc. 3 hours before p.m. test.....	12
Third day	
7.5 cc. 3 hours before a.m. test.....	11
7.5 cc. 3 hours before p.m. test.....	11
Fourth day	
7.5 cc. 3 hours before a.m. test.....	20
7.5 cc. 3 hours before p.m. test.....	24
Fifth day	
7.5 cc. 3 hours before a.m. test.....	31
7.5 cc. 3 hours before p.m. test.....	27
A five day pause occurred during which no extract of adrenal cortex was administered and no tests of behavior were made	
Eleventh day	
7.5 cc. 3 hours before a.m. test.....	28
7.5 cc. 3 hours before p.m. test.....	19
Twelfth day	
7.5 cc. 3 hours before a.m. test.....	22
7.5 cc. 3 hours before p.m. test.....	15
Thirteenth day	
7.5 cc. 3 hours before a.m. test.....	16
7.5 cc. 3 hours before p.m. test.....	11

* The time interval between conditioned stimuli was seven minutes.

cortex, which meant, of course, a corresponding increase in the relative amount of epinephrine. We sought, therefore, to determine what effect epinephrine alone would have on the behavior of the animals in order to analyze the problem systematically.

The general procedure in the second series of experiments was repeated. Normal sheep 11 and neurotic sheep 8 were employed. Each animal was given 5 cc. of a 1 : 200,000 solution of epinephrine daily in two subcutaneous injections of 2.5 cc. each. The tests of behavior were always made three hours after an injection. In the case of sheep 11 the critical tests were given for four days and in that of sheep 8 for five days. On the latter animal a test was made on the sixth day, one day after the administration of epinephrine had ceased.

In the case of neurotic sheep 8 a period of two months was allowed to elapse between the end of the last experiments and the beginning of the present series.

During this time sheep 8 was tested only occasionally in the laboratory, and in these tests the nervous condition showed a slight improvement as compared with the behavior during the preceding year and with that shown in the control tests of the first experiments. The animal became somewhat more manageable and cooperative.

The results obtained in the present series showed clearly that the vigorous reactions were not due to the action of epinephrine. During the administration of this substance the vigor of the reaction was not increased; it was, instead, noticeably decreased. Indeed, the whole behavior picture was almost exactly the opposite of that seen during the first experiments with extract of adrenal cortex. When the magnitude of the conditioned reflex diminished, the signs of the neurosis in sheep 8 became a great deal more evident.

TABLE 5.—*Effect of Repeated Small Doses of Epinephrine on the Magnitude of the Conditioned Motor Reflex in Normal and Neurotic Sheep*

	Normal Sheep 11	Neurotic Sheep 8
Average magnitude in mm. of the conditioned motor reflex during tests of 2 days preceding administration of epinephrine (16 stimuli)	254	211
Average magnitude of the conditioned motor reflex in each test period during administration of epinephrine (4 stimuli in each test)		
First day		
2 cc. 3 hours before a.m. test	107	237
2 cc. 3 hours before p.m. test	67	262
Second day		
2 cc. 3 hours before a.m. test	97	151
2 cc. 3 hours before p.m. test	99	148
Third day		
2 cc. 3 hours before a.m. test	148	78
2 cc. 3 hours before p.m. test	134	120
Fourth day		
2 cc. 3 hours before a.m. test	137	175
2 cc. 3 hours before p.m. test	99	121
Fifth day		
2 cc. 3 hours before a.m. test	...	211
2 cc. 3 hours before p.m. test	...	144
Sixth day		
A.M. test	...	...
P.M. test	...	231*

* The test period was not preceded by injection of epinephrine on this day.

In both animals the defensive reaction to the buzzer became lethargic. Each movement was, in the majority of tests, slowly executed and of noticeably smaller amplitude. That is, the foot was raised only a few inches from the platform. The flexion movements of the forelimb were also relatively few during the stimulation.

In neurotic animal 8 the spontaneous limb movements became increasingly frequent. The character of each movement underwent no noticeable change.

The results are shown quantitatively in tables 5 and 6. In table 5 the diminution in the magnitude of the conditioned reflex can be seen for both the normal and the neurotic animals. The decrement is noticeable for normal sheep 11 in the first test period, while for neurotic sheep 8 it is not seen till the first test of the second day. The maximal diminution appears in the second test of the first day for normal sheep 11 and in the first test of the third day for neurotic sheep 8. The maximal average decrease in the value of the reflex is more than 200 per cent for sheep 11 and more than 100 per cent for sheep 8. After the maximum is reached the values tend to approach the preliminary standard. They continue low for normal sheep 11 till the end of the experiment, but for

neurotic sheep 8 the level of the control value (211 mm.) is reached in the first test of the fifth day. The test on the neurotic animal 8, carried out one day after the last injection of epinephrine, shows an average reading for the magnitude of the reflex slightly higher than the standard.

Table 6 shows that the average number of the spontaneous leg movements was increased for neurotic sheep 8. It was doubled in the second test of the first day, and on the following day it was well above that of the level used as a control for that animal. The greatest number occurred on the second test period of the fifth day. But in the test made one day after the last injection the average number was the same as that in the preliminary control tests.

As in the preceding experiment the increase in the frequency of the nervous movements of the left forelimb was accompanied by other symptoms of an aggra-

TABLE 6.—*Effect of Repeated Small Doses of Epinephrine on the Number of Spontaneous Movements of the Forelimb in a Neurotic Sheep During the Rest Interval Between Stimuli*

	Sheep 8
Average number of spontaneous movements of limb per interval during tests of 2 days preceding administration of epinephrine	**10**
Average number of spontaneous movements of limb per interval in each test period during administration of epinephrine (3 intervals in each test)	
First day	
2.5 cc. 3 hours before a.m. test	10
2.5 cc. 3 hours before p.m. test	21
Second day	
2.5 cc. 3 hours before a.m. test	16
2.5 cc. 3 hours before p.m. test	19
Third day	
2.5 cc. 3 hours before a.m. test	19
2.5 cc. 3 hours before p.m. test	13
Fourth day	
2.5 cc. 3 hours before a.m. test	18
2.5 cc. 3 hours before p.m. test	16
Fifth day	
2.5 cc. 3 hours before a.m. test	20
2.5 cc. 3 hours before p.m. test	**23**
Sixth day	
A.M. test	..
P.M. test	11*

* The test period was not preceded by injection of epinephrine on this day.

vated general state of nervousness in sheep 8. Touching the forelimb always evoked the defensive reaction previously described and also, as in that test, a light touch on the abdomen would sometimes elicit it. Outside the laboratory the animal exhibited again every sign of the greatest excitement and lack of cooperation.

Normal sheep 11 remained perfectly quiet throughout the entire experiment, no sign of nervousness appearing at any time.

A typical graphic record of the behavior of neurotic animal 8, obtained after the administration of the epinephrine was begun, is shown in figure 1 *D*. The relatively "weak" reactions to the sound of the buzzer are shown, the movements being of small amplitude and relatively few. On the other hand, in this tracing the frequency of the spontaneous limb movements and the disturbance in breathing during the seven minute rest interval are much greater than those shown in tracing *B*. In a comparison of tracings *C* and *D* (fig. 1) it is noticeable that the behavior picture obtained with epinephrine is almost the exact opposite of that with extract of adrenal cortex.

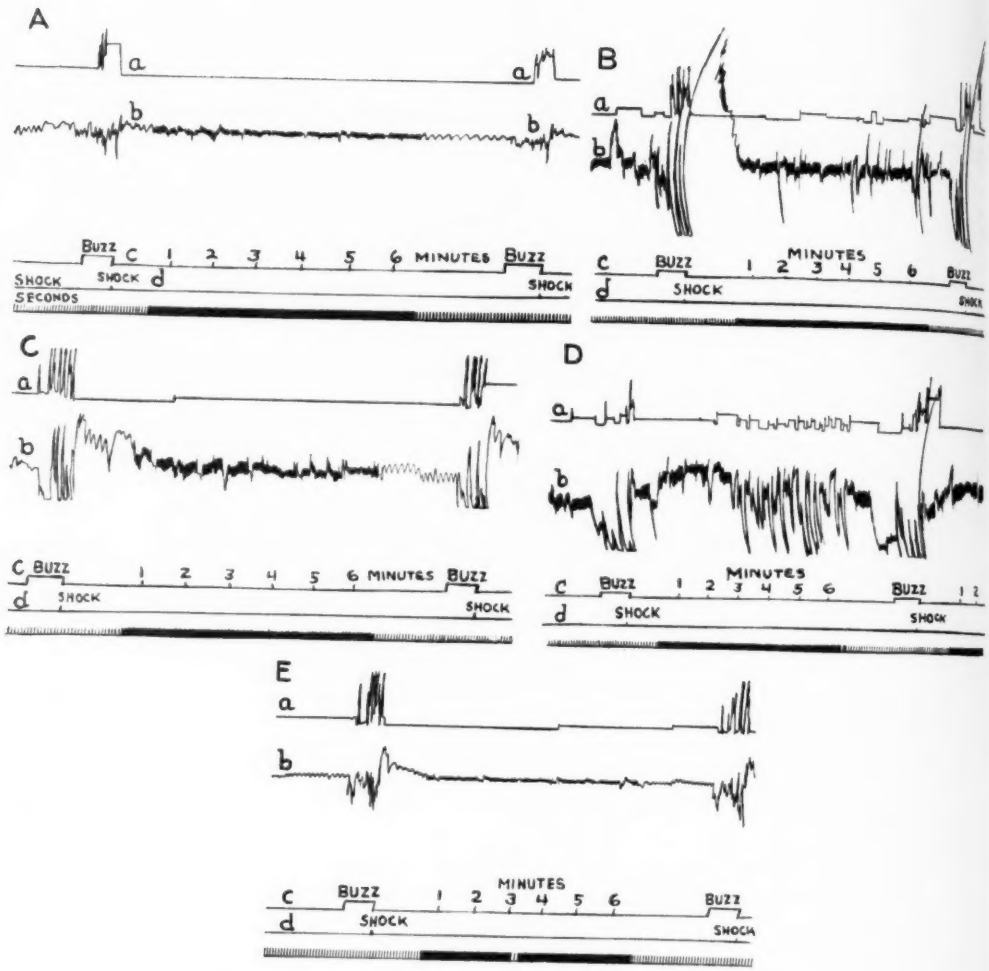
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Figure 1

EXPLANATION OF FIGURE 1

Fig. 1.—Typical records of the behavior of normal and neurotic sheep. *A*, tracings for normal sheep 11, showing the brisk conditioned defensive reflex of the left foreleg obtained on the sounding of a buzzer followed by a shock to the leg. Two presentations of the buzzer separated by an interval of seven minutes are shown. The animal remained quiet and respiration was slow and regular during the interval. The speed of the drum was reduced.

In this tracing and in the accompanying tracings *a* represents the reflex obtained for the left foreleg; *b*, the respiratory movements obtained during the same period, and *c* and *d*, the application of the conditioned stimuli by means of the buzzer (*c*) and the electric shock (*d*). The interval between applications of the stimuli is represented in minutes on tracing *c*. The record below represents the speed of the kymograph, expressed in seconds.

B, tracings for neurotic sheep 8 under the same experimental conditions as those for the normal animal, showing the conditioned reflex. It may be observed that the animal was extremely restless and nervous before and during the interval between the stimuli, as evidenced by spontaneous movements of the reacting limb and by the greatly disturbed respiration.

C, tracings showing the effect of therapy with extract of adrenal cortex on the reflexes of neurotic sheep 8. (The record was taken from those for series 4.) The extreme vigor of the conditioned reaction to the buzzer, as shown by the increased amplitude and number of the flexion movements of the limb and by the shortened latent period of the reaction, is indicated. A striking quieting effect can be seen in the interval. It may be noted that only one spontaneous movement of the leg occurred and that the respiration was relatively undisturbed.

D, tracings showing the effect of epinephrine on the behavior of neurotic sheep 8. This record may be compared with that shown in *C* and *B*. The "weak" conditioned reaction to the buzzer and the great increase in nervousness in the interval, as evidenced by the marked frequency of the spontaneous movements of the leg and by the exceedingly disturbed respiration, are to be noted.

E, tracings showing preservation of the effect of extract of adrenal cortex on the behavior of neurotic sheep 8 twenty-four days after therapy had ceased. (The record was taken from those for series 4.) The vigorous conditioned reactions to the buzzer, the relative quiet of the animal in the interval and, particularly, the undisturbed, calm respiration are to be noted.

It may well be that the action of epinephrine opposed or antagonized that of the adrenal cortical extract in the first two experiments. It may have masked or suppressed the effect of the cortical extract in such a way that only a temporary beneficial effect of the substance was evident, as seen in the tests on neurotic sheep 8 and A in the first series. In the case of the first animal, neurotic sheep 8, during the experiments of series 2 in which the larger amounts of cortical extract (15 cc. a day) were used, it is reasonable to suppose that the action of the extract was almost entirely superseded during the later phase of the experiment by that of the increased amounts of epinephrine (in the extract of adrenal cortex) and that as a final result the animal became more nervous than before the experiment. In the next series we sought to test this hypothesis.

SERIES 4.—We planned a new series of experiments on neurotic sheep 8 designed particularly to see whether the extract of adrenal cortex would have a more lasting effect on behavior if we administered an extract containing the least possible trace of epinephrine.

In this experiment the procedure was somewhat different from that in the experiments of series 2. A new lot of extract of adrenal cortex, containing epinephrine in a concentration of 1 : 500,000 instead of 1 : 200,000, as in the earlier series, was now administered. The amount was reduced from 15 to 10 cc. a day and was given subcutaneously in two injections of 5 cc. each. Three hours after each injection a test of behavior was made. The extract was given for eleven days. The tests were made, however, only on alternate days. This was done because we wished to run no risk of rendering the animal more nervous by overtesting. This frequency of testing was about the same as that which we employed in previous experiments with the nervous animals, and we have found it safe, as already stated.

Two weeks elapsed between the end of the last experiment with epinephrine and the beginning of this series. During that period routine tests of behavior were made from time to time, which revealed no improvement in the neurosis.

As a control the animal was this time tested twice daily on three of five days just prior to the administration of the extract.

Observations of the sheep's behavior during the critical period of the administration of "purified" extract of adrenal cortex showed clearly, first, that the vigor of the conditioned reaction was again greatly augmented and, second, that the animal became definitely less nervous. It became clear, further, that the effect was cumulative, as in the earlier series, but that, as was not the case in these experiments, it did not diminish with the continued administration of the cortical extract.

Graphs showing the absolute values for the magnitude of the conditioned reflex and the number of spontaneous leg movements between stimuli throughout the experiment are presented in figures 2 and 3.

In figure 2 each bar represents the magnitude of the conditioned reflex expressed in millimeters (during a ten second stimulation with the buzzer). In this graph it can be seen at a glance that the magnitude of the reflex underwent considerable augmentation as the tests progressed during the administration of the extract of adrenal cortex. The increase was not evident until the test on the afternoon of the third day (second day of testing). It was still more evident on the seventh day, although the magnitude of the reflexes had shown a diminution on the fifth. On the eleventh day, the last day on which the extract was given, the greatest increase was seen, the magnitude of the reflex reaching a value of

880 mm. When this value is compared with the greatest value reached in the control period, 365 mm., the extent of the augmentation becomes apparent.

The vigor of the reflex was still considerably augmented twenty-four days after the last injection of the extract, as can be seen in the record for a test made at that time.

In figure 3 each bar represents the number of spontaneous movements of the leg occurring in each seven minute interval between stimuli. Their frequency noticeably diminished on the ninth and eleventh days, and in the test made twenty-four days after the last injection the movements were still relatively infrequent. However, the movements did not disappear entirely at any time, as can be seen.

In comparing figures 2 and 3 it is again evident that the magnitude of the reflex and the number of nervous movements of the leg are inversely related. The more vigorous the reflex, the smaller the number of spontaneous movements.

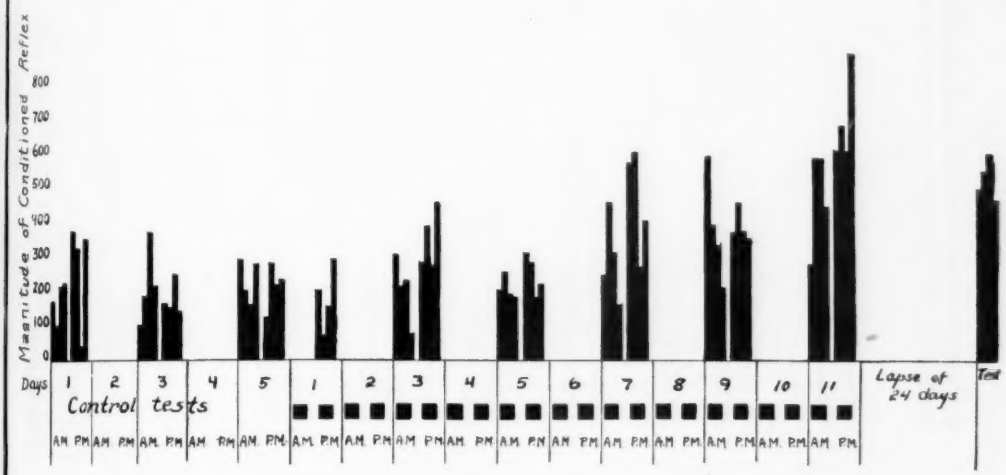

Fig. 2.—Graph showing the effect of therapy with extract of adrenal cortex on the magnitude of the conditioned motor reflex for neurotic sheep 8. In this and in the following graph the solid squares indicate the injection of 5 cc. of extract of adrenal cortex. Each test was made three hours after an injection. The results in the tests made on the first, third and fifth days of the control series were obtained before the administration of the extract. The preservation of the effect twenty-four days after therapy had been discontinued is to be noted.

From the seventh day onward, observations of the animal's general behavior showed a definite improvement in the nervous condition. As in the first series of injections of extract of adrenal cortex, it could easily be seen that the sheep was becoming quieter, not only during the laboratory tests but outside the experimental room as well. In the room it finally took interest in the food which was always placed before it, and during the intervals it would occasionally eat from the bucket, although never from the hand. It usually watched alertly all movements of the experimenter. Again, as in the earlier experiment, the reaction to touching the forelimb became difficult to elicit on most occasions, although occa-

sionally it was evoked. Outside the laboratory the animal was much less excited during the last few days of the tests. The calming effect of the dosage could be noticed, especially while the animal was being brought to the room. The neurotic sheep could be approached in the barn and would stand quietly while the leash was put about its neck, and it often would walk slowly and calmly to the laboratory. No violent struggling was seen at this time. It is of importance, too, that this relatively quiet general behavior was evident twenty-four days after the experiment. How long the effect lasts we do not know, since after the twenty-fourth day no further observations were made. It must be said, however, that although the quieting effect was pronounced, the animal did not exhibit at any time the calmness and friendliness characteristic of the perfectly normal and

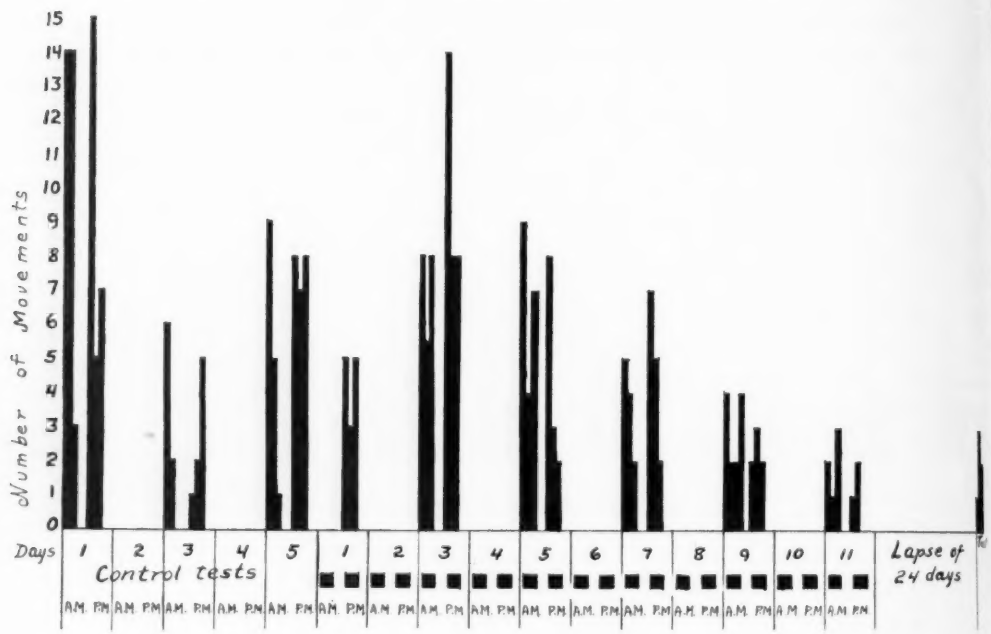

Fig. 3.—Graph showing the effect of therapy with extract of adrenal cortex on the number of spontaneous movements of the foreleg for neurotic sheep 8. The preservation of the effect twenty-four days after therapy had been discontinued is apparent. This chart was prepared from the data obtained in the same experiment on which the graphs in figure 2 were based.

well behaved sheep. It remained apparently somewhat suspicious of the laboratory room and of us.

In figure 1 the tracings *C* and *E* were obtained in the present experiment. Tracing *C* was selected from those made during the tests on the eleventh day. Tracing *E* shows the behavior picture for this nervous sheep twenty-four days after the last administration of the extract.

It is fairly certain from these results that the greater magnitude and permanency of the calming effect were due to the administration of the more highly purified extract of adrenal cortex.

COMMENT

It seems reasonable to suppose that the changes in behavior observed during the administration of extract of adrenal cortex, namely, the definite increase in the vigor of the conditioned reflex for all the animals and the coincident decrease in general nervousness of the neurotic animals, are true effects of the physiologic action of the substance. The facts that the vigor of the reflex was augmented for neurotic sheep 8 consistently (in all three experiments attempted with the animal) and that in two of the experiments (series 1 and 4) the nervous condition was considerably relieved, lend support to this view. It is also of significance that in the case of the two neurotic animals (sheep 8 and A) an injection of physiologic solution of sodium chloride substituted for one of extract of adrenal cortex failed signally to increase the magnitude of the reflex. A further experiment as a control was carried out with sheep A in which the entire procedure of series 4 was duplicated, and in this test 10 cc. of physiologic solution of sodium chloride was given each day in two injections of 5 cc. each in place of extract of adrenal cortex. Owing to the limitation of space we cannot report the results of the experiment in detail in this paper. Suffice it to say that during the repeated administration of the saline solution no change in the behavior of the animal took place.

In the neurotic sheep the apparently inverse relationship of the magnitude of the reflex and the number of nervous movements of the leg presents a problem. The facts seem to be somewhat contradictory. One would expect on first thought that each type of movement would be affected by the extract of adrenal cortex in the same way, since the substance has been shown to increase the tone and vigor of the neuromuscular system. One would expect a greatly augmented conditioned reflex to be followed by exceedingly frequent spontaneous movements of the reacting limb in the interval between stimuli—a period of great excitation to be followed by one of equally great excitation, not by a period of calm.

The facts may be more readily understood if the spontaneous movements of the leg are conceived of as affording the disturbed animal a means of relieving a state of nervous tension characteristic of the neurosis. They may act as a sort of spillway or safety-valve for "nervous tension." This tension and its resulting mode of expression in slight movements may arise originally through the habitual restraint of bodily movement necessitated by the conditions under which the animal's behavior is observed, namely, confinement to the restricted area of the experimental platform. The very act of restraining the movements may be responsible directly for the particular mode of expressing the presence of nervous tension observed in these

animals. When extract of adrenal cortex is administered to such an animal the strong and at times violent reaction which results serves in itself as a means of partially or wholly relieving the tension. Consequently, little or no relief is necessitated by spontaneous movements. They accordingly diminish in number, and in some cases they disappear altogether.

When epinephrine is injected, on the other hand, the reduced or weakened reaction cannot even partially serve as a means of relieving the tension; and the result is excessively frequent spontaneous movements of the "conditioned" forelimb.

Other questions arise from a consideration of the results. What is the intimate physiologic mechanism by which extract of adrenal cortex produces these effects on behavior? How does epinephrine bring about the opposite effects? Are these hormones truly mutually antagonistic? Why are the effects on behavior both of extract of adrenal cortex and of epinephrine cumulative? To attempt to answer these questions satisfactorily would, of course, be futile at present. Indeed, the answer to them can come only through further experiments designated more especially to study the physiologic modes of operation of the substances under the conditions which we have set forth in the preceding pages.

The experiments with sheep bear out the results obtained with the human subject, viz., that normal persons suffering from nervous tension or mental stress and from certain clinical conditions accompanied by nervous and mental symptoms are improved by the administration of extract of adrenal cortex.[8] Irritability is replaced by calm; sleep becomes more restful, and a greater resistance to fatigue develops. As these effects are partly subjective in man, there might be some doubt as to the factor of suggestion. The observations on sheep, being entirely objective, establish firmly the effects of extract of adrenal cortex on the nervous system. That the effect is exactly the opposite of that of epinephrine is most striking and may be significant.

In addition to the facts which we have presented concerning the influence of extract of adrenal cortex on an experimentally produced neurotic condition in sheep, the experiments have, we believe, demonstrated the possibility of studying and analyzing with accuracy many of those complex factors which play on and influence the activities of the central nervous system, normal and abnormal. In other words, there is here an experimental animal—"a laboratory preparation," as it were—in which one can observe the influence of the external environmental situation (the problem or predicament with which the animal finds itself confronted) and that of the internal environment (a resultant of the biologic life processes) on the mode of action of the nervous

system (just as the pharmacologist can observe and record the influence of certain drugs on the blood pressure of an animal preparation). This fact may be of significance not only to those especially interested in studies of animal behavior but to clinical psychologists and psychiatrists as well.

SUMMARY

A definite and enduring nervous disturbance, or neurosis, in sheep, produced by the method of the conditioned motor (defensive) reflex, is described. It is characterized chiefly by extreme excitement, uncooperative behavior and spontaneous, nervous, twitching movements of the limb concerned in the reaction.

The administration of an extract of the adrenal cortex to animals in this condition was found to increase the vigor of the conditioned reaction of the limb to a great extent and at the same time to decrease the frequency of the nervous movements of the leg, i. e., to quiet the animals. Improvement in the other symptoms of the disturbance was seen.

The conditioned reflex in normal sheep was also found to increase in vigor during the administration of the extract. The results obtained with extract of adrenal cortex in sheep bear out those observed in the human subject.

The repeated administration of epinephrine in a concentration of 1:200,000 was observed to have an effect on behavior exactly the opposite of that of extract of adrenal cortex. Epinephrine decreased the vigor of the conditioned reflex in both the normal and the neurotic animals, and in the latter animals it aggravated the nervous condition.

When extract of adrenal cortex relatively free from epinephrine was administered the beneficial effects were greater and cumulative. Moreover, they persisted for more than twenty-four days after the last injection.

An approximately quantitative method of analyzing the muscular activity of the animals was employed.

POSSIBLE RELATION OF LEAD INTOXICATION TO MULTIPLE SCLEROSIS

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Lead is a ubiquitous substance and, as pointed out by Dingwall and McKibben,[1] may be found in plants growing on soil containing lead. One should therefore recover lead from human excreta after the ingestion of foods containing this substance. Analysis of the feces of persons who have had no unusual exposure to lead shows 0.08 mg. per gram of ash.[2] Rabinowitch, Dingwall and Mackay[3] stated that, while the finding of lead in the feces does not mean that lead has been absorbed, urinalysis over a period of ten years at the Montreal General Hospital revealed that in unselected cases the average lead content of the urine is 0.1 mg. per liter. These results have been corroborated by others, and it is the consensus that the difference between the lead content of the excreta in health and that in disease is quantitative and not qualitative.

Attention was drawn to lead as a possible etiologic agent in cases of multiple sclerosis by the report of Cone, Russel and Harwood[4] at the meeting of the American Neurological Association in May 1933. A patient who had been painting in his spare time and in whom retrobulbar neuritis had developed was found to show lead in the urine and feces, and an attempt to eliminate the lead produced rapid ascending myelitis. Investigation of the spinal fluid (by the Fairhall[5] method) revealed the presence of lead. Calcium administered to bind the free lead stopped the degenerative process, and lead disappeared from the excreta, but decubital ulcers and urinary infection caused death. Lead was found in the bones, liver, brain and spinal cord. While the patho-

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Read at a meeting of the Chicago Neurological Society, Dec. 20, 1934.

From the Department of Nervous and Mental Diseases, Northwestern University Medical School.

1. Dingwall, A., and McKibben, R. R.: Unpublished data cited by Rabinowitch, Dingwall and Mackay.[3]

2. Kehoe, R. A., and Thamann, F.: The Excretion of Lead, J. A. M. A. **92**:1418 (April 27) 1929.

3. Rabinowitch, I. M.; Dingwall, A., and Mackay, F. H.: Studies on Cerebrospinal Fluid: II. The Occurrence of Lead in Cerebrospinal Fluid, J. Biol. Chem. **103**:725, 1933.

4. Cone, William; Russel, Colin, and Harwood, R. U.: Lead as a Possible Cause of Multiple Sclerosis, Arch. Neurol. & Psychiat. **31**:236 (Feb.) 1934.

5. Fairhall, L. T.: Lead Studies: VIII. The Micro-Chemical Detection of Lead, J. Biol. Chem. **57**:455, 1923.

logic lesions in the spinal cord were more extensive than those occurring in cases of multiple sclerosis, typical sclerotic patches were found in the cerebrum and cerebellum. In one patient with multiple sclerosis lead was found in the spinal fluid, and in another patient it was found in the spinal cord. No chemical tests had been carried out on the spinal fluid or urine in the latter case. A fourth patient, a man who handled leaded silks, testing the color for fastness by moistening the silk with his tongue, showed lead in the urine and spinal fluid; in addition there were stippled cells in the blood. The neurologic picture was that of multiple sclerosis.

In three other patients with the clinical picture of multiple sclerosis lead was found in the spinal fluid and urine. It may be noted that in all of the patients with multiple sclerosis mentioned lead was still pres-

TABLE 1.—*Cases Reported by Cone, Russel and Harwood*

Type of Case	Number of Cases	Lead Present	Lead Absent
Lead poisoning (neuromyelitis optica)	1	1	0
Multiple sclerosis	8	6	2
Multiple sclerosis suspected	1	1	0
Lesion of brain stem or spinal cord	4	4	0
Tumor of brain suspected	4	4	0
Infectious polyneuritis	1	1	0
Intracerebral hemorrhage	1	1	0
Chronic myositis	1	1	0
Neuromyelitis optica	1	0	1
Retrobulbar neuritis	1	0	1
Cerebral thrombosis	3	0	3
Lesions of the pyramidal tract with osteo-arthritis	3	0	3
Epilepsy	6	1	5
Hysteria	1	0	1
Psychoneurosis	1	0	1
Essential hypertension	1	0	1
Trichiniasis	1	0	1
Posttraumatic headache	1	0	1
Totals	40	20	20

ent in the urine and spinal fluid after calcium had been administered. Two other patients with this disease, but of the nonremitting type, showed no lead.

The spinal fluid of forty patients was investigated by Cone, Russel and Harwood, and twenty specimens showed lead while twenty did not.

Many have suspected that multiple sclerosis is due to a metallic toxin. Putnam [6] in 1883 found lead in the urine of patients with diffuse lesions of the brain and spinal cord; Berger [7] in 1905 reported that of

6. Putnam, J. J.: On Certain Unrecognized Forms of Lead Poisoning and on the Possibility of Mistaking Bismuth for Lead in Urine Analyses, Boston M. & S. J. **109**:315, 1883; Lead Poisoning Simulating Other Diseases, J. Nerv. & Ment. Dis. **10**:466, 1883.

7. Berger, A.: Eine Statistik über 206 Fälle von multipler Sklerose, Jahrb. f. Psychiat. u. Neurol. **25**:168, 1905.

206 cases of multiple sclerosis five were in lead workers. Eichhorst[8] in 1913 described a typical case of multiple sclerosis in a lead worker. Autopsy confirmed his diagnosis.

The chemistry of lead in the body, as described by Aub, Fairhall, Minot and Reznikoff,[9] lends itself well to the thesis that this substance may be a cause of multiple sclerosis. Lead may be stored in the body at any time during life; in fact, it is possible to demonstrate lead by roentgenograms of the ends of long bones of many of the patients in whom its presence is not suspected. Any tendency to acidosis liberates calcium. This throws lead into the circulation. On the other hand, feeding calcium salts or foods rich in calcium or overcoming the acidotic state tends to bind the lead. The remissions and exacerbations in cases of multiple sclerosis might be explained by the alternate freeing and binding of lead in the body. Since pregnancy and lactation tend to mobilize calcium, the exacerbations of multiple sclerosis so common during these periods could thus be explained.[4]

It has always been a problem how to demonstrate lead in the presence of organic matter such as is found in the cerebrospinal fluid. The first record of such a test is that of Marie,[10] who in 1908 reported a case of "lead meningitis." Trillat by means of a colorimetric estimation was able to demonstrate lead in the spinal fluid and later in the brain. Real progress in the detection of lead for clinical purposes was made when Fairhall applied the delicate Behrens and Kley[11] hexa-nitrite reaction to biologic material. This is the test that was used by Cone, Russel and Harwood. The chief difficulty, however, is not the failure to find lead when it is present but the finding of it as a result of contamination when it is not present in the original material.

Rabinowitch, Dingwall, and Mackay[12] checked the Fairhall procedure by using a meticulous technic and compared the results with those obtained by spectrographic analysis. They stated that the hexanitrite reaction was satisfactory provided the reagents were proved to be completely free from lead. They placed the sensitivity of the reaction at 10^{-4} mg. and that of the spectrographic method at from 10^{-5} to 10^{-6} mg. in 6 cc. of spinal fluid. The latter method has the advantage of

8. Eichhorst, H.: Bleivergiftung und Rückenmarkskrankheiten, Med. Klin. **9**:201, 1913.

9. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Medicine **4**:1, 1925.

10. Marie, A.: Cerveau de paralytique général saturnin, Bull. et mém. Soc. méd. d. hôp. de Paris **25**:104, 1908.

11. Behrens, H., and Kley, P. D.: Mikrochemische Analyse, ed. 3, Leipzig, Leopold Voss, 1915, p. 93.

12. Rabinowitch, I. M.; Dingwall, A., and Mackay, F. H. Studies on Cerebrospinal Fluid: I. Chemical and Spectrographic Detection of Lead, J. Biol. Chem. **103**:707, 1933.

requiring no reagents that might act as contaminants. They analyzed the spinal fluid in fifty cases by the combined methods. The numbers of crystals in cases other than those of lead poisoning were few. Twenty of the patients who had shown no lead were then rendered acidotic by the administration of ammonium chloride. The carbon dioxide-combining power generally dropped about from 15 to 20 volumes per cent. The urine showed an increased excretion of lead, and in five patients in whom the spinal fluid had been free from lead, the results became positive. Again in the patients who showed positive results

TABLE 2.—*Cases Reported by Rabinowitch, Dingwall and Mackay*

Type of Case	Number of Cases	Lead Present	Lead Absent
Lead poisoning	10	10	0
Patient a lead worker	1	1	0
Lead poisoning suspected	2	0	2
Cerebral arteriosclerosis	1	0	1
Cord lesion (?)	2	0	2
Disseminated sclerosis	27	2	25
Epilepsy	1	0	1
Patient normal	1	0	1
Peripheral neuronitis	2	1	1
Tabes dorsalis	1	1 (?)	0
Retrobulbar neuritis	2	0	2
Totals	50	15	35

TABLE 3.—*Cases Reported by Rabinowitch, Dingwall and Mackay in Which the Spinal Fluid Was Originally Lead-Free*

Type of Case	Number of Cases	Number Showing Lead During Acidosis
Cerebral arteriosclerosis	1	0
Cord lesion (?)	2	1
Disseminated sclerosis	12	2
Epilepsy	1	0
Peripheral neuronitis	2	1
Retrobulbar neuritis	2	1
Totals	20	5

small numbers of crystals were found as compared with patients known to have been poisoned by lead.

The present paper is based on analyses made in twenty-eight cases from the private practice of Dr. Lewis J. Pollock and from the neurologic clinics of the Northwestern University Medical School and the Mandel Clinic of the Michael Reese Hospital. The diagnoses were all confirmed by Dr. Pollock. The fluid was received in carefully acid-cleansed pyrex tubes, sealed with corks covered with paraffin which when tested showed no lead.

The Fairhall hexa-nitrite test was invariably conducted with three specimens: (1) a blank, (2) the unknown (about 6 cc.) and (3) a

known made up with a synthetic or real spinal fluid to which had been added a minute crystal of lead acetate.

METHODS

Technic.—The 5 or 6 cc. of cerebrospinal fluid in each crucible was evaporated to dryness over a water bath, about 1 cc. of redistilled nitric acid being added to help destroy the organic matter. The dry ash was placed in a muffle furnace at 450 C. for from two to four hours. The crucibles were always covered during the process. The ash was dissolved in 2 cc. of twice-normal hydrochloric acid. The solution was then neutralized with a 20 per cent solution of sodium hydroxide and brought to the point at which it was just acid to methyl orange. Hydrogen sulphide was passed through slowly for twenty minutes, and then the tube was corked and permitted to stand overnight. The mixture was centrifugated and the supernatant fluid poured off. The precipitate was washed four times with 0.1 per cent hydrochloric acid, saturated with hydrogen sulphide and centrifugated and decanted after each washing. To the residual precipitate was added 2 drops of redistilled nitric acid, and the tube was heated in a water bath until all the hydrogen sulphide was driven off. Slides were then prepared by the Fairhall technic. Only silica slides were used. A drop of each specimen was dried on a slide, and to it was added 5 cu. mm. each of sodium acetate and copper acetate. The dry material dissolved at these additions, and the mixture was recrystallized. The ring of salts was about 4 mm. in diameter. The slide was chilled on ice for about ten minutes, and to the residue was added 5 cu. mm. of a 10 per cent solution of acetic acid and a small crystal of lead-free potassium nitrite. No difficulty was encountered in recognizing the crystals of potassium-copper-lead hexa-nitrite.

Urine.—Analyses were carried out by the chromate method.[13] The lead was precipitated by entrainment with the phosphates on addition of 50 cc. of concentrated ammonium hydroxide per liter of urine. Three day specimens of urine were used. The residue was dried and digested several times in nitrohydrochloric acid (lead-free) and placed in the muffle furnace overnight at 450 C. Another digestion in the nitrohydrochloric acid mixture was necessary before a second period in the furnace produced a clear white ash. This was dissolved in hydrochloric acid, neutralized and brought to the point just acid to methyl orange, after which hydrogen sulphide was passed through for twenty minutes. The tube was corked and permitted to stand overnight. Then it was centrifugated, the supernatant fluid decanted and the residue washed four times with a 0.1 per cent solution of hydrochloric acid saturated with hydrogen sulphide. The residue was dissolved in nitric acid, the hydrogen sulphide driven off by boiling, and the mixture neutralized with sodium hydroxide and brought slightly acid to phenolphthalein by the addition of a 5 per cent solution of acetic acid. The lead was precipitated by adding 1 cc. of a 1 per cent solution of potassium chromate. The precipitate was washed carefully with hot water until it gave no pink color with di-phenyl carbazide (1 per cent in glacial acetic acid). The chromate was dissolved in hydrochloric acid, a solution of potassium iodide and soluble starch were added, and the liberated iodine was titrated against thousandth-normal sodium thiosulphate.

Comment.—In all the procedures silica crucibles with covers and silica slides were used. All glassware and tubes were of pyrex. The acids and water were

13. Fairhall, L. T.: Lead Studies: I. The Estimation of Minute Amounts of Lead in Biological Material, J. Indust. Hyg. **4**:9, 1922.

redistilled. The sodium hydroxide was kept in a paraffin-coated pyrex flask, and all other reagent bottles were of pyrex glass. The potassium nitrite was crystallized according to the Fairhall method by adding silver nitrate to form silver nitrite and then reforming the potassium salt by adding potassium chloride. The filtrate containing the potassium nitrite was evaporated almost to dryness on a steam bath, and the crystals were pressed out between filter papers. All reagents were continuously tested for lead contamination. In the microchemical studies, hexa-nitrite crystals were never found in the blanks and were always found in the known controls.

The patient with multiple sclerosis in whose spinal fluid lead was found was a young girl who had been given intravenous injections of sodium iodide by another physician before she was seen by Dr. Pollock. Potassium iodide has long been used empirically in the treatment of patients with lead poisoning. Aub, Fairhall, Minot and Reznikoff [14] showed that potassium or ammonium iodide causes a definite increase

TABLE 4.—*Author's Cases*

Type of Case	Number of Cases	Lead Present	Lead Absent
Multiple sclerosis	16	1	15
Lead poisoning	1	1	0
Lead poisoning suspected	2	0	2
Epilepsy	2	0	2
Cerebral arteriosclerosis	2	0	2
Amyotrophic lateral sclerosis	1	0	1
Paget's disease	1	0	1
Birth palsy	1	0	1
Anxiety neurosis	1	0	1
Unknown	1	0	1
Total	28	2	26

of lead in the excreta of patients already showing lead and causes lead to appear in the excreta of patients who have previously shown none. They attributed the action to the iodide ion. Sodium iodide might well liberate lead, which is stored in small amounts by practically every one. There were very few crystals on the slide as compared with those for the patients known to show lead. The urine of this patient contained lead. The urine of the patient known to have lead poisoning showed 0.2 mg. of lead per liter. He had been employed in cutting down a lead-painted bridge with an acetylene torch and showed typical lead colic; stippled cells and a lead line on the gums had developed, but no neurologic symptoms. Yet his spinal fluid revealed the lead crystals in greater abundance than did the spinal fluid of the patient with multiple sclerosis.

Cone, Russel and Harwood found lead in patients with the remitting type of multiple sclerosis and none in those with the nonremitting type. They found lead in only six of eight patients with this disease.

14. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Lead Poisoning, Medicine Monographs 7, Baltimore, Williams & Wilkins Company, 1926, p. 105.

However, they recovered lead from the spinal fluid in all of four patients with other lesions of the brain and spinal cord and in all of four patients with suspected tumor of the spinal cord, as well as in other isolated cases.

Of the sixteen cases of multiple sclerosis reported here, fourteen were of the remitting and two of the nonremitting variety. The results are comparable to those of Rabinowitch, Dingwall and Mackay,[3] who reported finding lead in the spinal fluid of two of twenty-seven patients with multiple sclerosis and of one of two patients with peripheral neuronitis. They obtained questionably positive results for the patient with tabes dorsalis. They, too, found few crystals when there was no evidence of lead poisoning. Making the patient acidotic increased the incidence of these faintly positive results.

CONCLUSION

Specimens of cerebrospinal fluid from twenty-eight patients were analyzed for lead by the Fairhall hexa-nitrite method.

In one of sixteen cases of multiple sclerosis the fluid showed a positive result. The patient had been given sodium iodide, and the urine also showed lead.

Of twelve other cases of various conditions, in only one, a case of lead intoxication, were abundant crystals found in the cerebrospinal fluid. In this case there was 0.2 mg. of lead per liter of urine.

Taking all three studies into consideration, there is no adequate proof for, and ample evidence against, the theory that lead is an etiologic agent in cases of multiple sclerosis.

DISCUSSION

Dr. G. B. Hassin: The mere presence of lead in the central nervous system of patients with multiple sclerosis does not denote any causal relationship. One might as well claim that multiple sclerosis causes the presence of lead, which no person with normal intellect would do. The changes in the central nervous system caused by lead differ entirely from those observed in patients with multiple sclerosis, in whom the main change is the progressive demyelinization of the nerve fibers with their ultimate atrophy and the formation of patches of sclerosis. Such changes are not observed in patients with lead encephalopathies in which the main lesion is not in the nerve fibers but in the ganglion cells, associated with extensive proliferative mesodermal changes, such as the new formation of blood vessels.

Dr. George W. Hall: In my opinion the average test for lead in the urine is worthless, and I am glad to see the care that was taken in the method of obtaining the reaction. Recently I saw a patient with palsy of an axillary nerve, and the claim was made that it was due to lead. The urine had been tested, but I am sure the test was not made with the care that was emphasized by Dr. Boshes. I have protested repeatedly against the claim that the finding of an unusual amount of lead in the urine proves that lead was the etiologic factor in a case of palsies or paralysis of an axillary nerve.

RELATIONSHIP OF UNCONSCIOUSNESS TO CEREBRAL BLOOD FLOW AND TO ANOXEMIA

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AND
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It is well known that stoppage of the blood supply to the brain or the production of severe anoxemia results in unconsciousness and, if prolonged, in irreparable injury to nerve cells. In view of this fact, it is an easy assumption that all states of unconsciousness are due, wholly or in part, to a defect in the cerebral circulation or in the nutrition of nerve tissues. Although a subject of lively debate, the matter has remained largely in the field of speculation because of lack of direct information concerning physiologic disturbances of the cerebral circulation in the human subject. States of consciousness are difficult of determination in animals, even if anesthesia is not used.

Two methods of direct approach to the study of cerebral circulation in unanesthetized persons are now available, viz., analysis of the oxygen content of the blood leaving the brain and observations of changes in blood flow by means of a thermo-electric blood flow recorder placed in an internal jugular vein.

We have already used one or both of these methods in studying the cerebral circulation with reference to the unconsciousness associated with normal or pathologic sleep [1] and with epileptic seizures.[2] In neither of these conditions was there evidence of a decrease in the total cerebral blood flow at the time consciousness was lost nor of an increase as consciousness was regained, so that we can now say with confidence that neither sleep nor epileptic seizures are due to reduction in the total cerebral circulation. There are, however, other conditions associated

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1. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: The Cerebral Blood Flow During Sleep in Man, Brain **58**:44 (March) 1935.

2. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, Arch. Neurol. & Psychiat. **32**:257 (Aug.) 1934.

with unconsciousness in which evidence of impaired circulation may be expected.

In this communication we report observations on three such conditions: (1) syncope, spontaneous or induced; (2) anoxemia induced by breathing of nitrogen, and (3) a carotid sinus reflex in persons with an abnormally sensitive carotid sinus. In these conditions we sought to determine what changes occur in cerebral circulation (1) by measuring the flow of blood through the internal jugular vein and (2) by measuring the oxygen content of the blood leaving the brain. Our object was to discover, if possible, to what extent loss of consciousness in each of these conditions is related to a failure of the oxygen supply to the brain.

METHODS

The blood flow recorder used in these experiments has been described by one of us (Dr. F. A. Gibbs).[3] It consists of a fine wire stilet with an electrically heated tip. This stilet is inserted through a hollow needle into the lumen of the internal jugular vein. The needle and stilet are thrust into the internal jugular vein close to the point where it emerges from the skull. A constant electric current applied to the tip of the stilet heats it to a temperature slightly above that of the blood. The faster the blood flows, the cooler the tip becomes; the slower the blood flows, the warmer the tip becomes. The temperature of the tip is measured by means of thermojunctions in series with a galvanometer. The instrument records changes in the velocity of the surrounding stream. With the cross-section area of the stream remaining constant (as it must at the point where the internal jugular vein emerges from its bony canal) changes in velocity may be interrupted as changes in volume flow. The records of blood flow obtained furnish no absolute values for volume flow; they indicate only the direction and general magnitude of alterations in the volume flow. For further details concerning the use of the instrument, previous communications may be consulted.

Blood was obtained from an internal jugular vein by the method described by Myerson, Halloran and Hirsch,[4] except that the head was kept horizontal and every effort was made to avoid stasis. In order to avoid more than one puncture and to secure repeated samples without delay a stilet was left in the needle when blood was not being withdrawn. Blood was analyzed for oxygen and for carbon dioxide by the method and apparatus of Van Slyke.[5]

In order to know when subjects were unconscious they were asked, in some cases, to tap a telegraph key. In other cases decision rested on the subject's lack of response to questions and his amnesia for things said and done in the period of apparent unconsciousness. The subjects were mostly patients with a history of seizures. The nature of the experiment was explained to each, and each gave his consent to it.

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3. Gibbs, F. A.: A Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141 (Oct.) 1933.

4. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from the Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

5. Van Slyke, D. D.: Notes on a Portable Form of the Manometric Gas Apparatus and on Certain Points in the Technique of Its Use, J. Biol. Chem. **73**:121, 1927.

SYNCOPE

This group comprised eight patients. One patient had orthostatic syncope; another (made available by Dr. L. D. Trevett of the Massachusetts General Hospital) fainted whenever he held his breath and attempted to expire. Syncope was induced in the other subjects in one of two ways: (1) forcible compression of the subject's chest during full inspiration followed by sudden release and (2) administration of 3 grains (0.2 Gm.) of sodium nitrite and, after an interval of ten or fifteen minutes, elevation of the subject on a tipping table to an upright position.

We shall first consider the experiments with the blood flow recorder. Records during five faints in three subjects were secured. In all but one there was a sharp decrease in blood flow immediately preceding and accompanying the loss of consciousness. The one faint which was not associated with a sudden decrease in cerebral blood flow occurred after the cerebral blood flow had been falling gradually for ten minutes. The patient with orthostatic hypotension had a history of fainting attacks in which she would fall and lie unconscious for many minutes. Having her stand up did not produce very unusual blood pressure changes or fainting, but when she was placed on the tipping table devised and loaned to us by Drinker [6] and raised very slowly to the erect position her pulse pressure would fall to 10 or 20 mm. and her pulse rate would rise to 130 beats per minute, at which point she would lose consciousness and fall (unless supported).

Chart 1 shows a record made during an induced faint in this patient. In addition to records of respiration, of cerebral blood flow and of brachial systolic and diastolic blood pressure as indicated on the chart, the heart rate and sounds were noted by means of a stethoscope applied to the chest.

When a subject without circulatory disorder is raised quickly from the recumbent to the erect position the cerebral blood flow, in keeping with the systemic blood pressure, usually declines (F. A. Gibbs, Loman and Myerson [7]). During the period of elevation of this patient the cerebral blood flow first declined gradually, then fluctuated abnormally, increasing and then suddenly decreasing as though it were being maintained with more and more difficulty. Finally, there was a precipitate drop in blood pressure and in cerebral blood flow, and the patient fainted. The pulse could not be felt and even the cardiac sounds were inaudible. The patient was replaced in a reclining position and the circulation became normal, after which consciousness returned. A few minutes later the test was repeated. This time there was a prolonged decrease in blood flow lasting throughout the period of elevation. At the point of fainting there was a further sharp but relatively slight drop, and the blood pressure could not be obtained.

There were five subjects from whom blood was drawn during syncope; four had been given sodium nitrite and then placed erect (solid circular dots in chart 2) and one fainted when attempting to expire against a closed glottis (open circle in chart 2). The oxygen of the internal jugular blood was markedly reduced in the period approaching unconsciousness. In all five instances in which the subject was certainly unconscious the blood was from 11 to 24.5 per cent saturated (table). These were indeed the lowest figures encountered during

6. Hamilton, J. E.; Lichty, J. S., and Pitts, W. R.: Cardiovascular Response of Healthy Young Men to Postural Variations at Varied Temperatures, Am. J. Physiol. **100**:383 (April) 1932.

7. Gibbs, F. A.; Loman, L., and Myerson, A.: The Effect of Posture on Cerebral Blood Flow, Arch. Neurol. & Psychiat., to be published.

unconsciousness. After the horizontal position was resumed and the patients had regained consciousness, the oxygen saturation of the blood leaving the brain was normal. These observations leave no doubt that syncope is accompanied by decrease in the supply of blood to the brain.

Some doubt was felt as to whether during the syncope the lungs were performing their function properly. In three cases arterial blood was drawn from a femoral artery during syncope. The average oxygen saturation of 92 per cent was nearly normal. In these three cases the average arteriovenous difference was over 14 volumes per cent against a usual difference of about 8 volumes per cent. This indicates that the minute volume flow of blood through the cerebral vessels was reduced to approximately one-half normal (granting that the consumption of oxygen by the brain did not change), a stagnation anoxemia. The decrease in blood pressure that occurred was sufficient to account for a decrease in flow of this order.

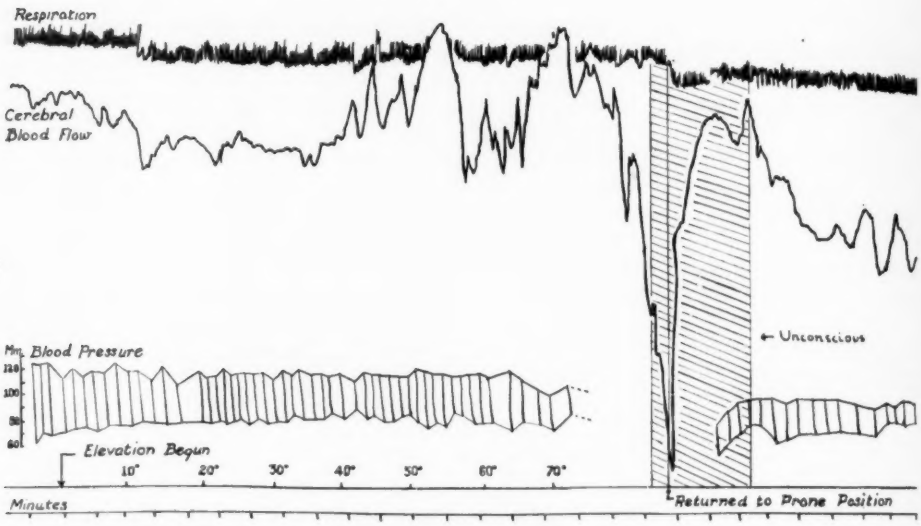

Chart 1.—The cerebral blood flow in a patient during orthostatic syncope. The patient was elevated from a prone position to an angle of 75 degrees in the course of sixteen minutes.

The top curve represents the patient's respiratory movements as transmitted from a pneumatic belt placed around the chest. The middle curve is a record of the cerebral blood flow. The perpendicular lines represent the blood pressure, the top of each line being the systolic and the bottom the diastolic pressure. The straight horizontal lines at the bottom represent the degrees of elevation of the tipping table and minutes of time, respectively. During the patient's elevation her systolic blood pressure decreased by 14 and her pulse pressure by 38 mm. of mercury. The hatched area covers the approximate period of unconsciousness, three and a half minutes. The perpendicular line within this area marks the return to the prone position.

The cerebral blood flow at first declined, then became very fluctuant with a higher than average normal flow. Then there was a sudden decrease, in the course of which the patient lost consciousness.

UNCONSCIOUSNESS CAUSED BY BREATHING OF NITROGEN

Unconsciousness was induced in a group of seven subjects by having them, while in the dorsal recumbent position, breathe from a rubber bag or a metabolism machine filled with nitrogen. Unconsciousness was produced in from one to two minutes.

Observations on two subjects by means of the blood flow recorder were in accord with the observations on milder degrees of anoxemia reported elsewhere by

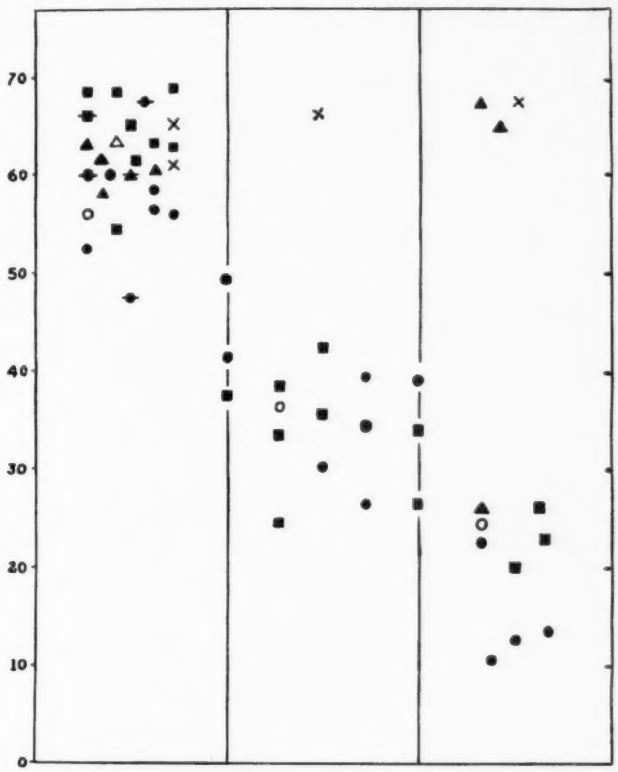

Chart 2.—The oxygen saturation of blood from the internal jugular vein with reference to the subject's state of consciousness.

The ordinates represent percentages of oxygen saturation. The abscissas divide the chart into three portions: The left-hand section contains values for the control (conscious) period, either before or after the experiment. In the latter case, the symbols are crossed by a horizontal line. The middle panel is for states approaching or bordering on unconsciousness; the right-hand one, for periods when the subject was unquestionably unconscious. When the exact status was questionable the results were placed on the division lines. The various symbols represent various experimental procedures, as follows: the solid circles, syncope induced by preliminary ingestion of sodium nitrite; the open circles, orthostatic syncope (one case); the solid squares, unconsciousness induced by breathing nitrogen; the solid triangles, unconsciousness due to the carotid sinus reflex; the cross, hysterical amnesia.

us.[8] During the development of anoxemia (and in spite of overbreathing which in itself reduces cerebral blood flow) the flow progressively increased. There was no significant change in the volume of the flow at the time consciousness was lost. In the case recorded in chart 3 the blood pressure also rose. The cerebral blood flow, however, did not constantly mirror the changes in the systemic blood pressure. With the subject again breathing room air and his consciousness restored, the flow fell to its previous level.

In five subjects blood was taken from the internal jugular vein at intervals during increasing anoxemia. Analysis revealed progressive decrease in the oxygen

The Gaseous Content of Internal Jugular and Arterial Blood with Reference to Consciousness

	Blood from Internal Jugular Vein									Arterial Blood		
	Conscious			Confused			Unconscious			Unconscious		
Type of Unconsciousness	Carbon Dioxide Content	Oxygen Content	Oxygen Saturation, per Cent	Carbon Dioxide Content	Oxygen Content	Oxygen Saturation, per Cent	Carbon Dioxide Content	Oxygen Content	Oxygen Saturation, per Cent	Carbon Dioxide Content	Oxygen Content	Oxygen Saturation, per Cent
Syncopal*												
1.....	50.72	10.18	53.5	51.10	8.68	49.5	52.42	6.77	38.6	42.55	16.08	92.9
2.....	50.52	10.68	56.1	51.45	6.44	34.6	52.12	2.04	11.0	39.88	16.72	90.0
3.....	52.23	10.57	57.0	.....	.....	....	54.42	2.47	13.0	40.70	16.85	91.0
4.....	52.39	11.34	59.5	50.58	5.10	26.7	50.44	2.57	13.4	42.03	17.90	94.0
5.....	55.80	12.45	56.1	59.01	8.21	36.7	61.04	5.41	24.5	.....	.....	....
Average	52.33	11.04	56.4	52.51	6.89	36.15	54.09	3.85	20.1	41.52	16.72	92.16
Caused by breathing nitrogen												
1.....	53.75	14.51	63.1	51.62	7.90	34.4	52.37	6.06	26.4	.....	.....	....
2.....	55.44	14.23	68.0	54.5	8.84	42.1	51.65	7.45	34.4	45.43	8.77	40.6
3.....	55.60	14.16	68.0	58.36	7.81	37.5	.....	.....	....	48.01	13.19	63.4
4.....	50.68	13.30	65.3	54.10	5.42	26.6	46.28	4.81	23.6	38.96	11.20	55.0
5.....	53.76	11.82	68.4	52.40	4.28	24.7	53.06	3.48	20.1	.....	.....	....
Average	53.85	13.60	66.6	54.89	7.01	33.5	50.83	5.45	26.1	44.13	11.05	53.0
Due to carotid sinus reflex†	41.82	10.17	62.0	42.95	8.62	32.4	44.70	4.05	25.0	.....	.....	....
Due to carotid sinus reflex‡												
1.....	53.87	11.65	60.5	.....	.....	....	51.04	12.90	67.0	.....	.....	....
2.....	51.03	11.03	62.8	.....	.....	....	50.31	11.17	63.7	.....	.....	....
Hysteria	56.45	14.03	65.0	53.94	13.96	65.0	53.15	14.55	67.0	47.30	19.94	92.05
Average	53.78	12.30	62.77	53.94	13.96	65.0	51.50	12.87	65.9	47.30	19.94	92.05

* In the first four patients syncope followed the use of sodium nitrite, the fifth fainted on attempted expiration.
† The patient had asystole during unconsciousness.
‡ These two patients had no fall of blood pressure.

saturation (table and the black squares in chart 2). When the subjects were cyanotic and approaching unconsciousness (in one case the subject may have been unconscious) the oxygen saturation of the venous blood lay between 25 and 42 volumes per cent. In one subject unconsciousness was not reached. In the three subjects who were certainly unconscious the values were between 20 and 26 volumes per cent. This anoxemia was not so extreme as that in syncope. The

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol. **111**:557 (April) 1935.

average oxygen content of the internal jugular blood was lower in syncope by 1.6 volumes per cent. However, in the fainting subjects the average carbon dioxide content of the internal jugular blood was higher by 3.3 volumes per cent (table). Increase of the carbon dioxide aids the dissociation of oxygen from the blood and increases the amount of oxygen available for use by the tissues. This therefore tended to equalize the tissue oxygen tension in the two conditions.

The arterial blood drawn during unconsciousness caused by breathing nitrogen showed, of course, a high degree of lack of oxygen. In three cases the average oxygen content of the arterial blood was 11 volumes per cent, or an oxygen saturation of 53 per cent. The arteriovenous difference in two cases, 3.8 volumes per cent, was less than the usual difference. This is in accord with data previously obtained by two of us (Lennox and E. L. Gibbs [9]). The small oxygen loss from the blood in its passage through the brain indicates (and the flow recorder corroborates) an increase of cerebral blood flow, not a decreased utilization of

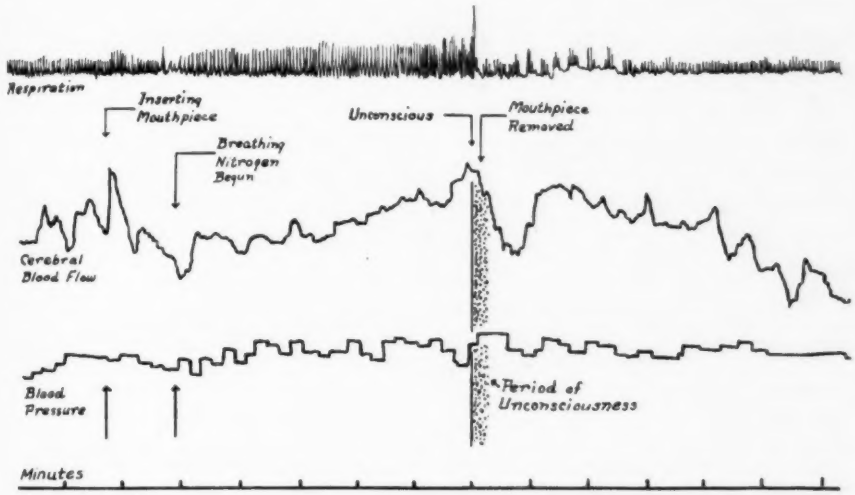

Chart 3.—Unconsciousness associated with the breathing of nitrogen.

The upper curve represents respiration; the middle one, cerebral blood flow, and the lower one, systolic blood pressure. During unconsciousness (dotted area) the pressure rose to 20 mm. above the control level. The period of five minutes required to produce unconsciousness was unusually long because of the fact that the subject was rebreathing into the tank of the machine for measuring basal metabolism, previously filled with nitrogen, whereas in other experiments subjects breathed from a bag and exhaled into the room. The unconscious period lasted only from the point indicated to a few seconds after removal of the mouth-piece. During the progressive increase in the patient's oxygen debt the cerebral blood flow was increased, and during unconsciousness the flow was higher than in his conscious state. The depth of respiration increased progressively, with a post-anoxemic period of periodic breathing.

9. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and Leg of Man, and the Changes Induced by Alteration of the Blood Gases, J. Clin. Investigation **11**:1155 (Nov.) 1932.

oxygen by the brain. By this increased flow the body apparently tries to keep the blood which passes through the brain as nearly arterial as possible. In oxygen lack, blood flow in the extremities may be decreased at the same time that the flow in the brain is increased, thus giving the brain a preferential supply.[9]

UNCONSCIOUSNESS CAUSED BY PRESSURE ON THE CAROTID SINUS

For many years it has been known that an occasional person will lose consciousness and have convulsive movements of the arms when pressure is applied over the carotid artery. Hill [10] quoted Kussmaul and Tenner as having described a group of six cases in 1857. The fainting was attributed to compression of the carotid artery with deficient supply of blood to the brain or else to stimulation of the vagus nerve. It is now accepted that the carotid sinus (perched in the crotch of the internal and external carotid arteries as they branch from the common carotid artery) is responsible for the faint.

Weiss and Baker [11] have studied the mechanism in a group of patients which now numbers more than thirty. They divide the cases into two groups: In the first group loss of consciousness is preceded by bradycardia or asystole and a fall of blood pressure. In the second group unconsciousness is not accompanied by evidence of circulatory failure. After denervation of the sinus in either group pressure applied over the sinus no longer produces loss of consciousness.

We made observations on seven patients, two of whom were kindly made available by Dr. Weiss. In four of the patients unconsciousness was preceded by bradycardia and hypotension; in three, it was not. The blood flow recorder (when used in the cases in which pressure over the sinus resulted in a fall of blood pressure and bradycardia) gave a record similar to that observed in syncope, that is, a sharp decrease in blood pressure and in cerebral blood flow preceding the loss of consciousness, with return of consciousness as the blood flow returned to its previous level (chart 4). Even in this class of patients with hypersensitivity of the carotid sinus, however, there were some in whom the decrease in cerebral flow seemed insufficient to account for the loss of consciousness since the decrease in blood pressure and in cerebral blood flow was not as great as could be produced by other procedures which did not cause loss of consciousness. One patient was tested who did not have a fall in blood pressure or bradycardia when pressure was applied over the carotid sinus, but who nevertheless became unconscious. He showed no decrease in cerebral blood flow preceding the loss of consciousness and a short but definite increase above the previous level during the period of unconsciousness (chart 5).

In five patients blood was obtained from an internal jugular vein during unconsciousness produced by pressure over the carotid sinus (solid triangles in chart 2 and last portion of the table). Dr. Weiss had previously found that the heart of

10. Hill, L.: Physiology and Pathology of the Cerebral Circulation, London, J. & A. Churchill, Ltd., 1896.

11. Weiss, S., and Baker, J. P.: Carotid Sinus Reflex in Health and Disease: Its Rôle in Causation of Fainting and Convulsions, Medicine **12**:297 (Sept.) 1933.

one of these patients remained at a standstill whenever pressure over the carotid sinus was being applied. In our experiment, blood drawn from the internal jugular vein of this patient while he was wholly unconscious was only 25 per cent saturated. The internal jugular blood obtained by Weiss and Baker [10] from three patients with bradycardia and hypotension were respectively 52, 56 and 66 per cent saturated. The absence of a profound degree of anoxemia in their patients may have been due to failure to secure the blood sample only during the few seconds of unconsciousness or it may have been due to the fact that these patients represent an intermediate type, one in which the reflex produces a decrease in cerebral blood flow, but a decrease which of itself would not be sufficient to produce unconsciousness.

In two of our patients loss of consciousness was not attended by bradycardia or fall in blood pressure. In these patients the oxygen content of the blood leaving

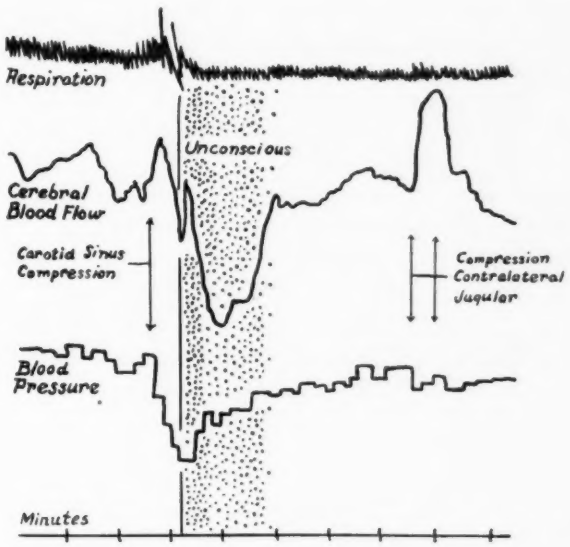

Chart 4.—The carotid sinus reflex with accompanying decrease in pulse rate and blood pressure.

The curves are the same as in chart 3.

Pressure of the right carotid sinus was applied at the point marked by the arrow on the left and continued until unconsciousness (dotted area) intervened. When carotid sinus pressure was applied to the right side it caused a compensatory increase in flow through the internal jugular vein of the left side, in which the flow recorder was inserted. At the end of the record pressure was applied over the right jugular vein in order to demonstrate an increase in flow not complicated by pressure on the carotid sinus. The first of the two arrows at the right indicates the application of the pressure; the second, its release.

Unconsciousness occurred during a precipitate fall in cerebral blood flow. The point at which consciousness returned was not clearly indicated in the protocol. The fall in blood pressure from the moment of applying pressure on the carotid sinus to the lowest reading which coincided with the loss of consciousness was 55 mm. of mercury.

the brain in unconsciousness was 0.7 volumes per cent greater than in the normal conscious state.

One patient who did not faint when given sodium nitrite had a hystero-epileptic seizure with apparent loss of consciousness and after recovery amnesia for the attack. He lay in a rigid cataleptic state, insensitive to painful stimuli. Blood taken at the onset of this state and again in the middle of it showed normal oxygen saturation. Likewise, blood drawn by us from the internal jugular vein of patients in status epilepticus had an oxygen saturation well within the range of normal.

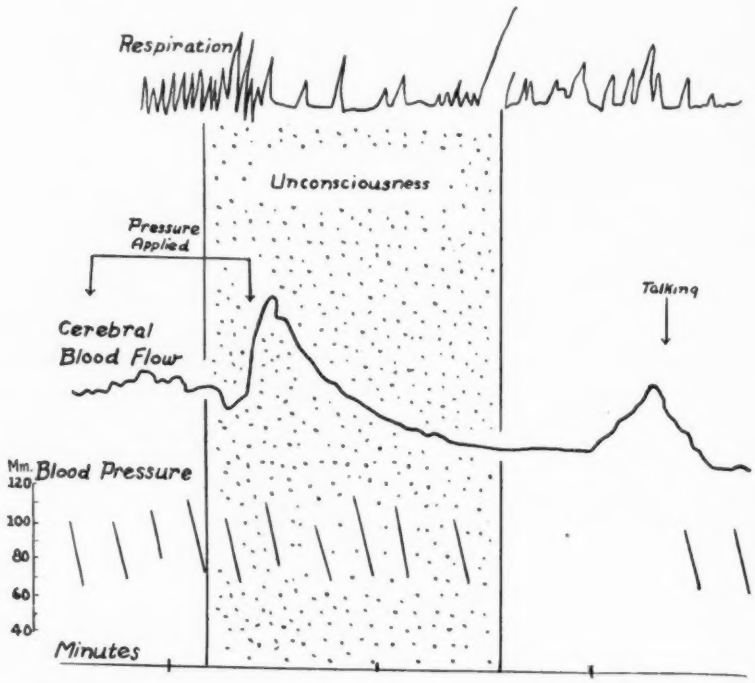

Chart 5.—The carotid sinus reflex with accompanying decrease in pulse rate and blood pressure. The curves are the same as in chart 1. The recording drum was moving much faster. The period of unconsciousness (dotted area) lasted a little more than a minute. During this time the only change was a temporary elevation of cerebral blood flow.

COMMENT

Our results in these twenty-two subjects make it possible to divide them into the following two groups: Those with spontaneous or induced syncope and those with unconsciousness from breathing nitrogen, also those with a carotid sinus reflex which produced bradycardia and a sharp fall in blood pressure. In all these subjects the unconsciousness might be attributed to defective blood or oxygen supply to the brain or, at least, to that portion of it which is concerned with consciousness.

Taking into consideration both the carbon dioxide and the oxygen content of the internal jugular blood, one concludes that the various types of unconsciousness in the first group must have been associated with approximately the same degree of oxygen lack in the brain substance. In every instance in which the subject was unconscious the blood leaving the brain was less than 30 per cent saturated; in every instance in which the blood was less than 24 per cent saturated the subject was unconscious. It is interesting to note that this degree of oxygen lack is not sufficient to prevent muscular activity. After the short severe muscular exercise of stair running the venous blood of the arm may be only 25 or 30 per cent saturated (Lundsgaard and Möller [12]).

The unconsciousness due to a stagnant blood supply (syncope) and the anoxic type (nitrogen breathing), as has been stated, did not differ greatly as regards the levels of oxygen tension if the lower level of carbon dioxide in the second type is taken into consideration (table). The two types differed markedly in the symptoms produced. Associated with syncope there were distressing giddiness, sweating, perhaps nausea and sometimes postsyncopal headache. Certain of these symptoms were undoubtedly related to the attempt of the subject to maintain proper cerebral blood pressure by shutting down on the flow through the skin and viscera. The subject's face became pale and his muscles flaccid. The unconsciousness resulting from the breathing of nitrogen, on the other hand, developed without unpleasant symptoms; in fact, the subject rarely knew that he had been unconscious. His face was livid, and there were rigidity of the jaws and oftentimes involuntary movements.

Cognizance should be taken of the fact that these experiments were all acute—the anoxia was quickly induced. It is possible that changes produced more slowly would give different results. This question will be discussed more fully elsewhere.[13]

In the second category were those of our patients whose unconsciousness was not associated with decreased blood flow through the brain, whose carotid sinus was involved and who did not have bradycardia or a fall in blood pressure. Since they could no longer be made to faint after the carotid sinus had been removed, the evidence suggests that in these patients we were dealing with a neural mechanism which can produce unconsciousness by some agency other than cerebral anoxia.

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12. Lundsgaard, C., and Möller, E.: Investigations on the Immediate Effect of Heavy Exercise (Stair-Running) on Some Phases of the Circulation and Respiration in Normal Individuals: I. Oxygen and Carbon Dioxide Content of Blood Drawn from the Cubital Vein Before and After Exercise, J. Biol. Chem. **55**:315, 1923.

13. Lennox, W. G.: The Constancy of the Cerebral Circulation, Arch. Neurol. & Psychiat., to be published.

From our data, then, it appears that there are two different mechanisms producing unconsciousness: (1) a deficient oxygen supply to the brain with direct impairment of the function of the nerve cells and (2) nerve impulses traversing certain pathways to the brain and producing unconsciousness by stimulation or inhibition of responsible areas. The conclusion does not necessarily follow, however, that these two mechanisms are mutually exclusive, for we may be dealing with a neurologic mechanism in both conditions. In the normal person, though an inadequate supply of oxygen to the brain will certainly impair or abolish cerebral function, a neuromechanism may be interposed which abolishes consciousness and postural reflexes as a means of avoiding more serious cerebral anoxemia. The loss of the standing posture and the compulsory cessation of exertion tend to improve the oxygen supply to the brain. Syncope may be a reflex which has survival value to the individual. In establishing the oxygen saturation of the blood perfusing the brain as unconsciousness supervenes we may simply have established the threshold at which lack of oxygen sets off a normal neural mechanism.

It is a question of considerable theoretical importance whether the unconsciousness of syncope and of nitrogen breathing occurs as the result of a reflex or whether it occurs because the central nerve cells have reached an oxygen tension below which they cannot function properly. Unfortunately, our evidence does not allow us to settle this matter. It is certain, however, that a 24 per cent saturation of internal jugular blood represents a general level of cerebral oxygen tension which, when suddenly arrived at, abolishes normal cerebral activity. On the other hand, the fact that pressure on a carotid sinus in certain persons will bring unconsciousness without preliminary cerebral anemia, together with the fact that cataplexy and reflex epilepsy occur without cerebral anemia,[2] points to the existence in man of a noncirculatory, probably neural, mechanism by which unconsciousness can be produced.

SUMMARY

The cerebral blood flow and the oxygen saturation of blood returning from the brain have been studied in twenty-two unanesthetized human subjects with reference to the loss of consciousness associated with (1) syncope (spontaneous or induced), (2) the breathing of nitrogen and (3) a hyperactive carotid sinus reflex. Two methods of judging cerebral blood flow were applied: (1) observation of the changes in the volume of flow as indicated by a thermo-electric blood flow recorder inserted in an internal jugular vein and (2) measurement of the oxygen saturation of blood leaving the brain through the internal jugular vein.

The observations permit the division of the subjects tested into two groups: First are those in whom unconsciousness was preceded by a

sharp fall in the volume of cerebral blood flow or was accompanied by a very low oxygen tension in the blood leaving the brain. In these cases the patient was always unconscious if the oxygen saturation in the blood of the internal jugular veins was 24 per cent or less. Second are those whose carotid sinus was involved and in whom there was no preliminary fall in blood pressure. These had neither decrease in cerebral blood flow nor decrease in the oxygen saturation of the blood leaving the brain.

CONCLUSIONS

1. In man unconsciousness supervenes if the oxygen supply to the brain is suddenly reduced to such an extent that the oxygen saturation of the blood in the internal jugular vein falls to 24 per cent or below. If it does not fall below 30 per cent the subject remains conscious.

2. Certain persons with a hyperactive carotid sinus reflex show loss of consciousness without marked diminution of cerebral blood flow, their unconsciousness resembling, in this respect, cataplexy and reflex epilepsy.

3. A mechanism exists by which transient loss of consciousness can be produced without the intervention of a general cerebral anoxia. This mechanism is probably essentially neural.

CAN THE PROBLEM OF THE NEUROSES BE FORMULATED MORE CONCISELY?

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Psychiatry has often been criticized by physicians working in other branches of medicine for the vague formulation of its problems. Critics, however, have perhaps not given due consideration to the fact that psychiatry has to deal with the many shades of thought and feeling, and that since these are so varied in nature words may prove inadequate to convey all that exists in a given case. In any science, however, as knowledge increases words may be better utilized to convey a picture of the true state of affairs. With this in mind regarding certain problems of the neuroses, it seems that the present knowledge of them is greater than definitions have yet set forth.

Psychoanalysis has shown the neuroses to be the result of social pressure on the individual person. This pressure exerts itself early in life, producing a neurosis in childhood or a psychic structure which may succumb to a neurosis later in life when the person unconsciously feels his early conflict being repeated. This view of the neuroses assumes them to be psychogenic, i. e., produced by way of the mind.

To some the foregoing statement is a truism; nevertheless, it is surprising how many practitioners of medicine in general and of psychiatry in particular are not adherents of this view. Some accept it in part, as in cases of obsessive-compulsive phenomena in which only the intellectual processes are involved, but the acceptance becomes less complete as one approaches the formation of symptoms as observed in cases of neurasthenia and hysteria. Others may accept this point of view in theory but not in practice, so that the physician, while telling the patient that his difficulty is due to mental conflict, nevertheless proceeds to treat him by physical means. Lastly, there are those who deny any psychic cause whatever and attempt to treat persons with neurosis on a physical basis alone.

The last group is a minority. There are few who do not believe that emotion plays some part. Hence, the issue is the degree of acceptance of an emotional etiology. In other words, the problem is not whether emotional factors within and social factors without produce the neurosis but to what extent this is true to the exclusion of other factors.

Read at the meeting of the Philadelphia Psychiatric Society, Oct. 12, 1934.

Problems of the neuroses are of more than academic importance. They are of great economic and social importance to the whole of society. The number of persons incapacitated by neuroses is tremendous. The same holds true of those with psychoses, but these patients are regarded by both physicians and laymen in quite a different light. It is readily accepted that the person with a psychosis cannot be a useful member of society for either a temporary or a prolonged period and that he may even need hospitalization or supervision. But the neurotic person, by being regarded as having a nonmental illness, may be responsible for many more sacrifices on the part of the family and the state than the patient with a psychosis, because the neurotic person is often looked on as potentially easily curable. It is true that most neurotic persons are potentially curable but the potential is variable, and the problem is not as simple as some would think, especially when adequate appreciation is not given to the mental aspect of the illness. In these cases the physician may not understand the mental side of the condition, or, understanding partially, he may nevertheless believe it inexpedient to apprise the patient or his relatives, because of the unwillingness of the average patient to accept such a view of his illness.

The attitude of the medical profession was until recently, and to a large extent is still, that the management of a neurosis is completed when the diagnosis is made. This is the same as saying that nothing is wrong; the patient is advised to forget his complaint and get back to active life. But the patient and symptoms usually return with irritating persistence. Then various hit-or-miss procedures are often followed: medication, use of electricity, massage, even suggestion or persuasion. Notwithstanding, the fundamental problem remains untouched: that of bringing the patient to terms with his immediate conflict with reality or with his inner problem resulting from a long previous conflict with reality.

The problem of the neuroses has been so vaguely formulated that one looks in vain in textbooks for a definition of neurosis. Students find great difficulty in grasping clearly what a neurosis is or how it differs from a psychosis. That difference is sometimes so minimal as to puzzle even the experienced psychiatrist, but this should not deter one from attempting to define the neuroses more clearly, if only for the reason that the more clearly outlined the objective the easier it is of attack.

Granted that a long definition is cumbersome and a short one often inadequate, might one not use the following formulation for practical purposes?

A neurosis is a clinical condition produced by unconscious mental conflict in which the manifestations may be symptoms of physical dysfunction, recurring thoughts, acts or affects which the subject regards

as serving no useful purpose but which he nevertheless cannot modify and in which the manifestations are accompanied by a subtle but definite disturbance in the integration of personality and in the ability to adapt himself to reality.

For those who would quarrel with this definition it should be stated that its purpose is partly to stimulate interest in the formulation of a better one. However, would not this definition cover the various types of neuroses, including neurasthenia, anxiety states, conversion hysteria, phobias and the obsessive-compulsive phenomena? Even also the conditions presented by the neurotic personalities—the swindlers, pathologic liars, thieves and others, who are often labeled psychopathic and neurotic personalities? The former term is perhaps more expressive but too inclusive. It fails to be specific if one accepts the structure of this group as similar to that of the neuroses.

To return to the definition: It is the disturbance in adaptation to reality in cases of neuroses which would seem to deserve special attention. To say that there exists a disturbance in the ability of the person to adapt himself to reality implies a disturbance in the proper appreciation of the relative values of reality, or, in short, a disturbed sense of reality. This condition has been tacitly accepted by psychiatrists for some time as present only in the psychoses.

Discussions in the textbooks on the difference between a neurosis and a psychosis are so detailed and statements based on them often so contradictory that it seems unfair to the authors to quote an isolated statement and inexpedient to quote from them at length. There are, nevertheless, those who contend that the differences between a neurosis and a psychosis are only quantitative, while others state that there are varying degrees of qualitative as well as of quantitative difference. But it is practically always agreed that a neurosis is a failure in adaptation to reality, while the same thing is said concerning a psychosis. In spite of this, a disturbed sense of reality has been cited as a differentiating feature rather than one common to the two conditions. An adaptation to reality is dependent on a proper sense or perception of reality. How can one have the disturbance in adaptation without the disturbance in appreciation of that to which one is to be adapted? Close study of the neuroses shows that to minimize the significance of a disturbance in the well balanced perception of the values of reality is to retard the recognition of an outstanding feature, since a distortion in the perception of the values of reality produces the neurosis and remains as part of the structure.

What does one mean by reality? It is the immediate and expected future environment to which the person must adapt himself with due regard for the structure of the society of which this environment is a part. On first thought, the word reality calls up a mental picture of

certain facts of daily life to which one adapts oneself without undue affect, such as male and female, day and night, summer and winter, sleeping and waking, work and play, love and hate, happiness and sadness, comfort and discomfort, pleasure and pain, and riches and poverty. But on closer examination one finds that a well balanced view of reality is never held by a person with a neurosis. Instead, one finds that the instincts of self-preservation and procreation are the sources of powerful emotional currents, which attach themselves to these apparently impersonal realities, transforming them into something of varying value to the self. This makes them personal, and it happens that personal demands may invest some of these realities with such intensity of affect that others are lost sight of, resulting in a distortion of values which will not adapt themselves to a fairly inflexible social structure.

It has been to a large extent taken for granted that in the neuroses conflict might arise, needing minor counsel or rearrangement of the environment. But not enough attention has been focused on the fact that these factors of reality have for the patient distorted affective values, which have been responsible for the conflict. Whether the sense of reality is well balanced or distorted is, after all, determined by the relative affective value invested in that which is perceived by the organs that register sensation. A well balanced attitude to these factors of reality in relation to the self requires careful teaching during psychic growth to prevent an affective imbalance in one direction, especially a persistence of childish disproportionate evaluations in a world demanding a broader, more impersonal, adult point of view. But it is recognized that such imbalances due to improper attitudes toward the environment do occur, and instances are familiar. But compensations for these distorted evaluations must result, and they are many and varied; they include repression, sublimation, rationalization, projection, displacement, formation of symptoms, etc. Some may represent an added distortion of reality, but this distortion, it must be remembered, is secondary and not primary. It is found that these compensations resulting in neuroses or psychoses are a matter of psychic dynamics and not a sudden static break with the adjustment to reality. In fact, even if one takes the more static point of view, one sees marked disturbances in the values of reality in the neuroses. The person with neurasthenia believes that his body is functioning poorly, in spite of careful studies by his most trusted physician. The patient with a compulsive neurosis sees a piece of money as a deadly carrier of disease as well as a medium of exchange. The patient with a phobia sees a street as a place of extreme danger to him and yet as a safe place of travel for all others.

These examples show distortion in the perception of the values of reality as well as in the adaptation to reality. The fact that the patient temporarily can correctly orient himself verbally in these respects does

not alter his behavior. In a case of simple schizophrenia or paranoia the patient may temporarily do this equally well.

The following quotation is taken from the translation of Fenichel's work: [1]

> But to recall what was said in regard to the withdrawal from the reality in neuroses: This withdrawal was a turning to phantasy, a process called introversion. The place of the real objects, from whom the patient turned in disappointment was taken by the phantasy objects of his childhood life. In other words, the orientation to objects was preserved. The patient declared his independence of reality, but supplanted it by phantasy, but he did not in fact free himself from object representations. There is not a complete withdrawal of the libido into the ego. As Abraham in his first communication definitely pointed out, the differential point between neuroses and psychoses depends on whether, in the process of withdrawal from reality, the object representations were preserved.

So it would seem that one should not limit the concept of the perception of reality too narrowly or make too static an orientation to it. Psychoanalytic study of persons with neuroses and psychoses has demonstrated that in the former group, fortunately for treatment, there is a greater capacity for transference, which means among other things that the patients have retained a greater capacity to deal with reality, but it indicates that a deficit in this quality is nevertheless present. One should be concerned rather with the direction taken in any departure from well rounded adult values of reality. This departure in the patient with a psychosis, being sometimes more mystic, more bizarre and more extreme, has received more attention, possibly because it appears so much more apart from that of every-day thought than any departure in the direction of the infantile. Undoubtedly, an unconscious sympathy with the infantile trends in the neurotic person causes many to overlook their presence.

It has been stressed that physicians in all departments of medicine, and not psychiatrists alone, must become acquainted with the neuroses and the neurotic personality. To overlook either is to retard medical advancement, because in so many disease conditions results of research, study and therapy are modified and even vitiated by an unrecognized psychic factor. If such an appreciation of the neuroses is to occur, it would seem necessary to withdraw the concept of a disturbed sense of reality as a diagnostic feature differentiating the neuroses and the psychoses and reapply it as one of the cardinal diagnostic conditions in the neuroses as well. This would involve no striking change—merely that what had been so apparent in some psychoses would be searched for more diligently in the neuroses, because it would be more subtly mani-

1. Fenichel, Otto: Outline of Clinical Psychoanalysis, translated by B. D. Lewin and G. Zilboorg, New York, W. W. Norton & Company, Inc., 1934, p. 339.

fested and require more acumen for its recognition. Such acumen may be compared with that required to discern between schizophrenia of the simple and that of the paranoid type. In short, the concept seems too valuable to be wasted on an occasional condition in the psychoses usually expressed as distortion of reality, which is after all only a special manifestation of a more general condition common to both neuroses and psychoses.

This would, of course, raise the problem of the standards of measurement. How is one to know what adaptation to reality compatible with health could be used as a guide? Glover [2] stated: "The normal individual is one who is free from symptoms, unhampered by mental conflict, has a satisfactory working capacity and can love someone other than himself."

Since the first two demands of this definition deal with the negative of a neurosis, one may center one's attention on the last conditions. These speak for themselves in their fundamental importance. Without a satisfactory working capacity the preservation of the self is threatened. Without a capacity to love the procreation of the self may be seriously threatened, either by despair and self-destruction or by inability to reproduce the self by sexual union.

Now these are discoverable faults in adaptation, even though their discovery may not be easy. It is possible for the physician to ascertain approximately the patient's capacity to work and to love, both these conditions to be regarded, of course, in their broadest sense. This would mean in the first instance the ability to work efficiently and with satisfaction to the self, and in the second the capacity to mobilize sufficient feeling toward one's fellow men to insure a satisfactory social relationship with them. Difficulties in these fields may be subtly concealed, but so are the signs and symptoms in many other disease conditions. Medicine has been tardy in recognizing what to look for in that group of conditions called neuroses. There is no longer doubt that in neuroses something definite is to be looked for in the field of the integration of personality and that there are certain standards of measurement with which to compare what is found.

Hence, one sees that it is frequently as necessary (and sometimes more so) for the physician to examine and test the adaptation to reality as to examine and test the function of the heart, lungs or kidneys. It should be justifiable for the professor in any department of medicine or surgery to ask the student: "What do you know about the function of the patient with regard to his adaptation to reality?" This concept would come to mean something definite to both physician and patient,

2. Glover, Edward: Medico-Psychological Aspects of Normality, Brit. J. Psychol. **23**:152, 1932.

and hence the examination would be carried out with more cooperation and dispatch.

How this can best be done is not the subject of this paper. Methods of approach to the neuroses are now being taught in certain medical schools with more or less thoroughness. But I believe that this teaching will be more successful if a change in thinking is brought about concerning the sense of reality. Some disturbance in a proper perception and appreciation of reality necessary for adaptation is always present in a neurosis, and the physician should be taught both to look for it and to evaluate it properly when found. For psychiatry to stress this point in regard to the neuroses would seem to be of real value to medicine in general.

SUMMARY

It is believed that some of the vagueness surrounding the neuroses can be removed and that they can be defined with greater accuracy, which will automatically set them more clearly apart from the psychoses and make understanding of them easier to the student.

A definition of the neuroses is proposed.

The problem of adaptation to reality in the neuroses is discussed in an attempt to show that a well balanced perception of the values of reality is lacking in these conditions as well as in the psychoses, and that the difference is one only of degree and subtlety of manifestation.

DISCUSSION

Dr. L. H. Smith: The distinction between neurosis and psychosis is difficult. Dr. English's discussion of the loss of the sense of reality in the neuroses is in contrast with the recent presentation of Dr. Yaskin of the same factor being present in definite depression. I agree with Dr. English that there is at times a possible disturbance of the sense of reality in neuroses, but it seems to me that if one finds this in a neurosis one must acknowledge that there is a certain movement or trend toward psychosis and that the disturbance should be considered indicative of the degree of illness rather than of the type. Such knowledge is important, likewise, from the standpoint of prognosis.

Psychoses and neuroses result from a struggle between the conscious and the unconscious. Greater success occurs in treatment of the neuroses than that of the psychoses because the conscious is not disturbed. In psychoses the struggle is the same, but the conscious is disturbed. In neuroses there are phenomena of substitution and compensation.

Dr. J. C. Yaskin: Dr. English has presented a new and important point of view for the evaluation of the neuroses and psychoses in relation to their diagnosis and treatment. The sense of reality is a component of the larger symptomatology of these conditions, and it is useful as a criterion in differentiating the neuroses and the psychoses. The diagnosis of neurosis does not necessarily indicate curability; the physician is familiar with the therapeutic failures in cases of the compulsion-obsessive states and the difficulties of management of the anxiety hysterias. Nevertheless, Dr. English's formulation helps in elucidating the several steps in the investigation and treatment of the neuroses, viz., the determination

of the rôle played by disturbances of the soma and the general chemism and the nature and depth of the underlying emotional conflict.

DR. O. S. ENGLISH: This study was stimulated by contact with physicians in other departments of medicine. Many cases of the neuroses may be overlooked through lack of appreciation of the disturbance of personality which always accompanies them. Psychiatry has the responsibility of making this important point understood.

EXPERIMENTAL CONVULSIONS INDUCED BY ADMINISTRATION OF THUJONE

A PHARMACOLOGIC STUDY OF THE INFLUENCE OF THE AUTONOMIC NERVOUS SYSTEM ON THESE CONVULSIONS

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The use of absinth in the production of experimental convulsions in animals was first devised by Marcé [1] in 1864; since that time it has been used extensively by numerous workers. Thujone is the chief constituent of the volatile oil of absinth which is obtained from the leaves of Artemisia absinthium (wormwood). It is a dextrorotatory ketone, thalviol tanacetone, with the formula $C_{10}H_{16}O$ (Sollmann,[2] Hackh [3]); it was first used as a convulsant by Cobb [4] in 1922, and since then by Florey,[5] Sparks,[6] Lennox, Nelson and Beetham,[7] Keith [8] and others.

Experimental convulsions brought about by the administration of thujone closely resemble true epileptiform seizures and have been shown to originate in the central nervous system. It has been repeatedly demon-

1. Marcé: Note sur l'action toxique de l'essence d'absinthe, Compt. rend. Acad. d. sc. **58**:678, 1864.

2. Sollmann, Torald: Manual of Pharmacology and Its Application to Therapeutics and Toxicology, ed. 4, Philadelphia, W. B. Saunders Company, 1932, pp. 188 and 194.

3. Hackh, I. W. D.: A Chemical Dictionary, Philadelphia, P. Blakiston's Son & Co., 1929.

4. Cobb, S.: Case of Epilepsy with General Discussion of the Pathology, M. Clin. North America **5**:1403, 1922.

5. Florey, A.: Action of the Convulsant Thujone, J. Path. & Bact. **28**:645 (Oct.) 1925.

6. Sparks, I.: Experimental Studies of Epileptic Convulsions, Arch. internat. de pharmacodyn. et de thérap. **35**:460, 1927.

7. Lennox, W. G.; Nelson, R., and Beetham, W. P.: Studies in Epilepsy: Factors Affecting Convulsions Induced in Rabbits, Arch. Neurol. & Psychiat. **21**:625 (March) 1929.

8. Keith, H. M.: The Effect of Various Factors on Experimentally Produced Convulsions, Am. J. Dis. Child. **41**:532 (March) 1931; Further Studies in the Control of Experimentally Produced Convulsions, J. Pharmacol. & Exper. Therap. **44**:449 (April) 1932.

strated by Gotch and Horsley,[9] Boyce,[10] Bouché,[11] Horsley,[12] Hill,[13] Elsberg and Stookey[14] and others that absinth affects particularly the intact large brain. It has also been shown that larger doses of the drug were required to produce convulsions in decorticated and spinal animals, and that the type of seizure was altered in them (Magnan,[15] Uyematsu and Cobb,[16] Sparks,[6] Davis and Pollock,[17] Pike and Elsberg[18]).

In addition to the motor phenomena numerous autonomic manifestations such as occur in clinical epilepsy accompany these experimental convulsions. Marcé[1] in his original communication mentioned involuntary defecation during absinth convulsions in dogs and rabbits. Boyce[10] described salivation and involuntary micturition in cats. Sparks[6] noted salivation, micturition, defecation, emesis and rapid respiration after the administration of thujone. Pike, Elsberg, McCulloch and Rizzolo[19] described in detail the following autonomic phenomena in cats given absinth in alcohol: salivation, dilatation of the pupils, blanching and injection of the mucous membranes, erection of the hair with bushing of the tail, increased secretion of sweat on the pads of the feet, involuntary micturition, increase in the respiratory rate and excursion, and protrusion of the penis. Florey[5] in a study of the changes in the blood pressure of cats after the injection of thujone

9. Gotch, F., and Horsley, V.: On the Mammalian Nervous System: Its Functions and Their Localization Determined by an Electrical Method, Phil. Tr. Roy. Soc. London, s.B **182**:267, 1892.

10. Boyce, R.: The Seat of Origin and Paths of Conduction of the Fits of Absinthe Epilepsy, Brit. M. J. **2**:1097 (Nov. 18) 1893.

11. Bouché, quoted by Horsley.[12]

12. Horsley, V.: On Dr. H. Jackson's View of the Functions of the Cerebellum as Illustrated by Recent Research, Brain **29**:446 (March) 1906.

13. Hill, L.: On Cerebral Anaemia and the Effects Which Follow Ligation of the Cerebral Arteries, Phil. Tr. Roy. Soc. London, s.B **193**:69, 1900.

14. Elsberg, C. A., and Stookey, B. P.: Studies in Epilepsy: I. Convulsions Experimentally Produced in Animals Compared with Convulsive States in Man, Arch. Neurol. & Psychiat. **9**:613 (May) 1923.

15. Magnan, V.: Recherches de physiologie pathologique avec l'alcool et l'essence d'absinthe, Arch. de physiol. norm. et path. **5**:115, 1873.

16. Uyematsu, S., and Cobb, S.: Preliminary Report on Experimental Convulsions: Convulsions Produced by the Administration of Chemical Substances, Arch. Neurol. & Psychiat. **7**:660 (May) 1922.

17. Davis, L., and Pollock, L. J.: Experimental Convulsions: Crucial Experiment to Determine the Convulsive Site, Arch. Neurol. & Psychiat. **20**:756 (Oct.) 1928.

18. Pike, F. H., and Elsberg, C. A.: The Occurrence of Clonic Convulsive Seizures in Animals Deprived of the Cerebral Motor Cortex, Am. J. Physiol. **72**:337, 1925.

19. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Rizzolo, A.: Some Observations on Experimentally Produced Convulsions, Am. J. Psychiat. **9**:259 (Sept.) 1929.

demonstrated a marked fall with slowing of the heart rate, an increase in the amplitude of the beat and an increase in the rate and depth of the respirations. Coombs and Pike [20] studied the respiratory and cardiovascular changes after giving absinth and noted both a fall in the blood pressure and an acceleration of the respiration.

The question of the rôle and importance of the autonomic nervous system in the epileptic discharge is one that has been extensively investigated in the modern study of epilepsy. The results are inconstant, however, and in spite of the amount of interesting work done in this field the whole problem is yet lacking in clarity.

Since the morphologic and functional studies of Gaskell [21] and Langley [22] and the more recent work of Loewi,[23] Dale,[24] Newton, Zwemer and Cannon,[25] Cannon and Bacq,[26] Rosenblueth and Cannon,[27] Babkin, Gibbs and Wolff,[28] Babkin, Alley and Stavraky [29] and many other investigators, the important rôle of pharmacologic agents as factors in the study and in the function of the autonomic nervous system is well recognized. Pharmacology has revealed a number of agents (the research is ably

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20. Coombs, H., and Pike, F. H.: Respiratory and Cardiovascular Changes in the Cat During Convulsions of Experimental Origin, Am. J. Physiol. **97**:92 (April) 1931.

21. Gaskell, W. H.: The Involuntary Nervous System, New York, Longmans, Green & Co., 1916.

22. Langley, J. N.: The Autonomic Nervous System, Cambridge, England, W. Heffer & Sons, Ltd., 1921.

23. Loewi, O.: Ueber humorale Uebertragbarkeit der Herznervenwirkung, Arch. f. d. ges. Physiol. **189**:239, 1921; **193**:201, 1922.

24. Dale, H. H.: The Action of Certain Esters and Ethers of Choline and Their Relation to Muscarine, J. Pharmacol. & Exper. Therap. **6**:147, 1914; Chemical Transmission of the Effects of Nerve Impulses, Brit. M. J. **1**:835 (May 12) 1934.

25. Newton, H. F.; Zwemer, R. L., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Organs: Mystery of Emotional Acceleration of Denervated Heart After Exclusion of Known Humoral Accelerators, Am. J. Physiol. **96**:377 (Feb.) 1931.

26. Cannon, W. B., and Bacq, Z. M.: Studies on Conditions of Activity in Endocrine Organs: Hormone Produced by Sympathetic Action on Smooth Muscle, Am. J. Physiol. **96**:392, 1931.

27. Rosenblueth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Organs: Some Effect of Sympathin on Nictitating Membrane, Am. J. Physiol. **99**:398 (Jan.) 1932.

28. Babkin, B. P.; Gibbs, O. S., and Wolff, H. G.: Die humorale Uebertragung der Chorda tympani-Reizung, Arch. f. exper. Path. u. Pharmakol. **168**:32, 1932.

29. Babkin, B. P.; Alley, A., and Stavraky, G. W.: Humoral Transmission of Chorda Tympani Effect, Tr. Roy. Soc. Canada, 1932, sect. 5, p. 89; Am. J. Physiol. **101**:2, 1932.

summarized by Rothlin [30] and by Fröhlich [31]) which have a most marked and specific effect on the peripheral mechanism of the autonomic nervous system. As generally recognized, some of these pharmaceutical preparations have an effect much the same as that of stimulation of the autonomic nerves. They may be grouped into: (*a*) sympathomimetic agents—epinephrine, ephedrine, beta-tetra-hydronaphthylamine and, in part, histamine and pituitary—and (*b*) parasympathomimetic agents—acetylcholine, acetyl-beta-methyl-choline, choline, pilocarpine and physostigmine. The last-named drug, besides having a preserving effect on the acetylcholine and acetylcholine-like substances in the blood stream (Loewi and Navratil,[32] Engelhardt and Loewi [33] and Matthes [34]), is a central parasympathetic stimulant, resembling in this respect the sympathomimetic beta-tetra-hydronaphthylamine (Rothlin,[30] Cloetta and Waser,[35] Bouckaert and Heymans,[36] Stern,[37] Régniers [38] and others).

Besides these stimulants there is a group of drugs which have a depressing effect on the autonomic nervous system. It has been known for a long time that atropine abolishes the effect of pilocarpine and many of the effects of stimulation of the parasympathetic nerves. More recently it has been shown by Dale [24] and others that it also abolishes the action of acetylcholine. To the same group as atropine belong hyoscyamine and scopolamine.

Pharmacology owes the discovery of ergotoxine chiefly to Dale [39] and Stoll.[40] It is an alkaloid which has the property of abolishing

30. Rothlin, E.: Zur Pharmakologie des vegetativen Nervensystems, Schweiz. med. Wchnschr. **43**:1001, 1930.

31. Fröhlich, A., in Bethe, A.; von Bergmann, G., et al.: Handbuch der normalen und pathologischen Physiologie, mit Berücksichtigung der experimentellen Pharmakologie, Berlin, Julius Springer, 1927, vol. 10, p. 1095.

32. Loewi, O., and Navratil, E.: Ueber humorale Uebertragbarkeit der Herznervenwirkung, Arch. f. d. ges. Physiol. **214**:678 and 679, 1926.

33. Engelhardt, E., and Loewi, O.: Fermentative Azetylcholinspaltung im Blut und ihre Hemmung durch Physostigmine, Arch. f. exper. Path. u. Pharmakol. **150**:1, 1930.

34. Matthes, K.: The Action of Blood on Acetyl Choline, J. Physiol. **70**:338, 1930.

35. Cloetta, M., and Waser, E.: Beiträge zur Kenntnis des Fieberanstieges, Arch. f. exper. Path. u. Pharmakol. **73**:436, 1913.

36. Bouckaert, J. J., and Heymans, C.: Beta-tetrahydro-naphthylamine et ergotamine, Arch. internat. de pharmacodyn. et de thérap. **35**:139, 1929.

37. Stern, Richard: Ueber die Wirkung der Hydronaphthylamine auf den thierischen Organismus, Virchows Arch. f. path. Anat. **115**:14, 1889.

38. Régniers, P.: Influence de la tétrahydronaphthylamine sur la température et les échanges respiratoires: Action antagoniste de la chloralose et de l'antipyrine, Arch. internat. de pharmacodyn. et de thérap. **35**:70, 1929.

39. Dale, H. H.: On Some Physiological Actions of Ergot, J. Physiol. **34**:163, 1906.

40. Stoll, A.: Mutterkorn, Naturwissenschaften **11**:697, 1923.

specifically the effect of stimulation of the sympathetic nerves, the effect of epinephrine and that of some other stimulants of the sympathetic nervous system. To the same group as ergotoxine belong quinine and yohimbine, though the effect of these is not so specific.

Separately in the group of paralyzing agents stands nicotine. As revealed by the studies of Langley and Dickinson,[41] this alkaloid after a transient excitation of the sympathetic nervous system produces complete paralysis of the same. This effect is due to its action on the autonomic ganglia, the paralysis when pronounced occurring in the parasympathetic as well as in the sympathetic division.

There are indications in the literature that some of these drugs can influence experimental convulsions. Rovighi and Santini [42] found that atropine increased the severity of convulsions brought about by the administration of picrotoxin. Notkin and Pike [43] noted the interesting fact that epinephrine combined with absinth increased the severity of the resulting fits. This observation was confirmed by Keith,[44] who found that small amounts of epinephrine decreased by 50 per cent the convulsant dose of thujone and that pitressin and pituitary had the same effect.

Considering these observations and the marked autonomic disturbances which occur during an experimental convulsion brought about by thujone, we thought it likely that agents other than the aforementioned group of pharmaceutical preparations would influence the experimental convulsions. A systematic study in this direction seemed advisable and has been undertaken in the present investigation.

METHODS

Unanesthetized rabbits and cats have been used throughout this work, and a statistical method, as suggested by Lennox, Nelson and Beetham,[7] has been applied in judging the results. The rabbit has been found to be more satisfactory than the cat in this type of experiment. Emotional activity interferes to a considerable extent with the action of thujone, and the struggling and fear attendant on intravenous injection in the cat often made difficult the interpretation of the results. Control experiments have also been carried out on rabbits, monkeys and cats anesthetized with ether, chloralose or dial. In these experiments the animals have

41. Langley, J. N., and Dickinson, W. L.: Pituri and Nicotin, J. Physiol. **11**:265, 1890.

42. Rovighi, A., and Santini, G.: Sur les convulsions épileptiques par les poisons: Recherches critico-expérimentales, Arch. ital. d. biol. **2**:279, 1882-1883.

43. Notkin, J., and Pike, F. H.: Some Experiments on the Effects of Caffeine, Adrenalin and Bromides upon the Susceptibility of Experimentally Induced Convulsions in Animals, Am. J. Psychiat. **10**:771 (March) 1931.

44. Keith, H. M.: Factors Influencing Experimentally Produced Convulsions, Arch. Neurol. & Psychiat. **29**:148 (Jan.) 1933.

been placed in Gage's headholder and records of the blood pressure, respiration, flow of blood through the submaxillary gland (Maevsky's[45] method) and observations of the pial blood vessels according to Forbes'[46] technic have been made.

The thujone was prepared as a 1 per cent emulsion in 6 per cent gum acacia, and given intravenously in amounts which would invariably produce a convulsion when given to the animal for the first time (viz., 0.4 cc. per kilogram for the unanesthetized rabbit, and 0.7 cc. per kilogram for the unanesthetized cat). The resulting convulsions varied from mild to severe and were graded from 1 to 4 as described previously by one of us (Keith). In anesthetized animals larger doses of thujone had to be used, the amount being variable. As a subminimal dose, one half of the convulsant dose of thujone was used. This dose alone produced only occasional slight convulsions in not more than 19 per cent of the unanesthetized animals, but when given with some of the activating agents it was sufficient to produce constantly severe fits.

RESULTS OF EXPERIMENTS

During the present investigation approximately three hundred injections of thujone have been given to rabbits and cats. The minimal convulsant dose and the inactive subconvulsant dose of thujone suspension have been carefully checked and found to be constant. There is general agreement among the many workers as to the type of convulsion produced by absinth or thujone. Those that we have produced are identical with the convulsions described by others (Marcé,[1] Magnan,[15] Sparks,[6] and Pike and his co-workers[19]).

In our unanesthetized animals the convulsions occurred within from thirty to sixty seconds after the injection of thujone and were sometimes ushered in by a cry. In cats this was at once followed by dilatation of the pupils, sometimes erection of the hair of the back and bushing of the tail, and by jerking of the ears and head, acceleration of respiration, clonic movements of the extremities and frequently salivation, micturition or defecation. If the dose of thujone was large a tonic phase might precede the clonic movements. The latter would then be violent and end in running movements, with the animal on its side. The rapid, deep respiration outlasted the muscular movements. The animal appeared dazed after the attack, but usually recovered within a few minutes and walked about.

In the rabbit the attack was very similar with the exception that the autonomic phenomena were perhaps less marked. There were frequently, however, slight dilatation of the pupils, salivation, defecation, occasionally micturition and always increased respiration. The muscular movements began as twitchings in the ears and head, later involving the limbs and trunk. In very sensitive rabbits or when large doses of thujone were used a tonic phase occurred almost immediately, in which the animal would become extremely rigid with limbs and head extended and back arched, the typical position of opisthotonos. Respiration was suspended for a short interval but was resumed when the clonic movements began.

45. Maevsky, V. E.: Sympathetic Innervation and Process of Normal Salivary Secretion, J. Physiol. **57**:307 (June) 1923.

46. Forbes, H. S.: Cerebral Circulation: I. Observation and Measurement of Pial Vessels, Arch. Neurol. & Psychiat. **19**:751 (May) 1928.

It was also possible under several general anesthetics, e. g., ether, dial and chloralose, with larger doses of thujone to produce typical convulsions which were accompanied by many of the aforementioned autonomic manifestations.

In figure 1 records of the effects of different doses of thujone on a cat under dial anesthesia may be observed. In *A* a subminimal dose of thujone was administered; the fall of blood pressure, dilatation of the pial artery, increased flow of blood through the submaxillary gland (chorda tympani and cervical sympathetic nerves intact) and increased respirations can be seen in the absence of a convulsion.

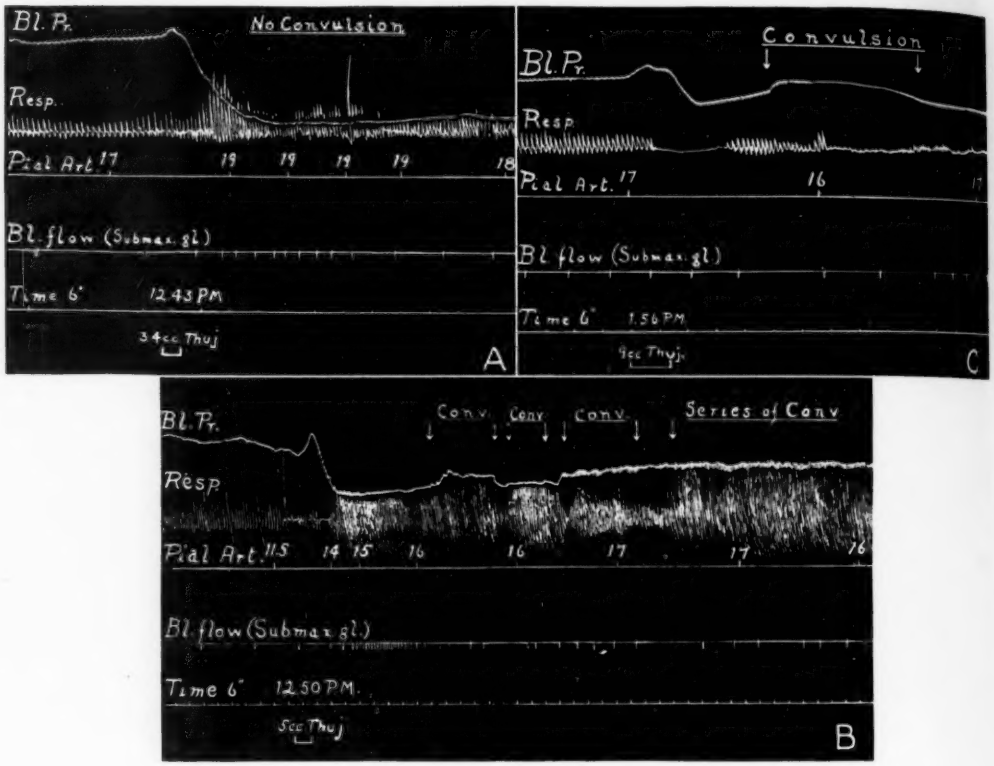

Fig. 1.—The effects of intravenous administration of different amounts of 1 per cent thujone: *A*, the effect of a subconvulsive dose (cat P549; 1.7 Kg.; 0.6 cc. of dial, intraperitoneally). *B*, a series of convulsions due to a single large dose (cat P551; 2.4 Kg.; 1 cc. of dial, intraperitoneally). *C*, the effect of a sublethal dose (cat P549; 1.7 Kg.; 0.6 cc. of dial, intraperitoneally).

The abbreviations used in this and the following figures are: *Bl. Pr.*, blood pressure (pial artery—basal line); *Resp.*, respiration; *Pial Art.*, diameter in units of pial artery (1 unit = 20 microns); *Bl. flow*, blood flow from the vein of the submaxillary gland; *Thuj.*, thujone; *C.* and *Conv.*, convulsions; *Hist.*, histamine; *Ac. chol.*, acetylcholine; *Epin.*, epinephrine.

In *B* a typical record of a series of several convulsions can be seen with all the aforementioned phenomena. The vasodilatation precedes the convulsions and

subsides during their continuance. It is of interest to note that immediately preceding each convulsion there is a transient decrease in the flow of blood through the submaxillary gland. This inhibition of the circulation was seen also in other instances, as in the tracing of the effect of thujone and epinephrine and is so evanescent that it could not be followed under the microscope in the pial artery.

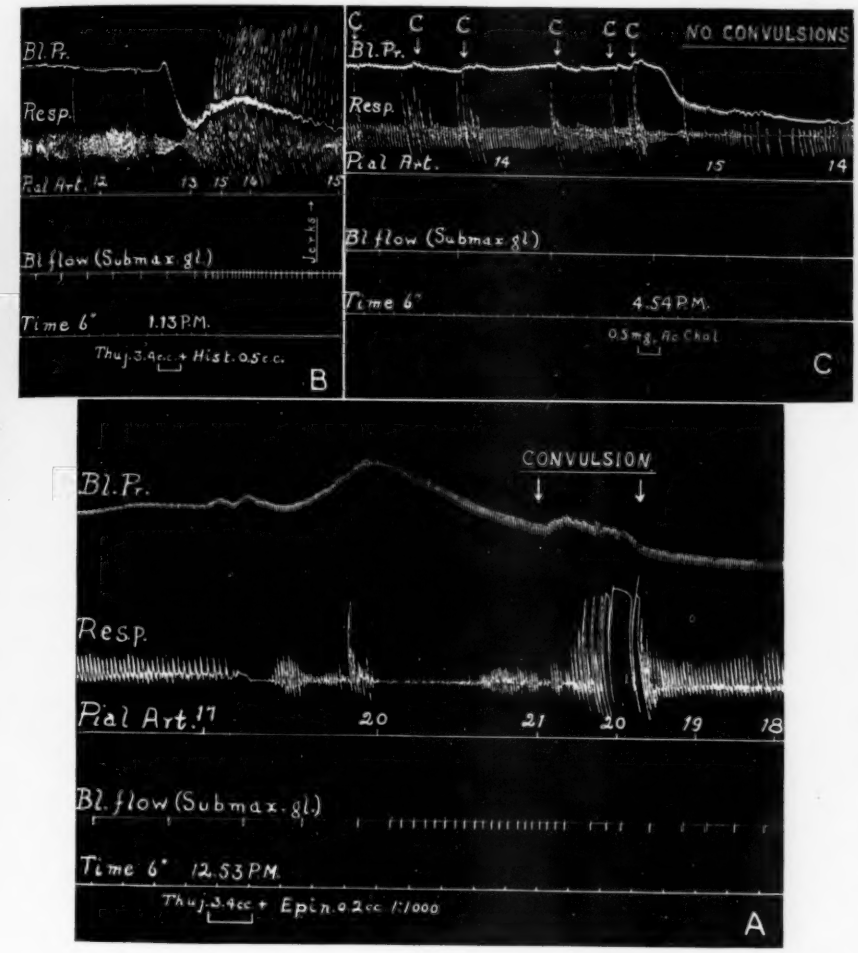

Fig. 2.—*A*, the effect of thujone combined with epinephrine (blood pressure elevated from 86 to 160 mm. of mercury); *B*, the effect of thujone combined with histamine (cat P551; 2.4 Kg.; 1 cc. of dial, intraperitoneally). *C*, status epilepticus due to repeated doses of thujone interrupted by acetylcholine (cat P550; 1.8 Kg.; 0.6 cc. of dial, intraperitoneally).

In *C* a convulsion was produced by a large sublethal dose of thujone, and instead of the increase in respiration and in the flow of blood an inhibition took place. This inhibition was particularly pronounced after previous injections of epinephrine hydrochloride.

In figure 2 the effects of several of the drugs combined with the thujone have been recorded in a similar way. In *A* the simultaneous effects of thujone and epinephrine in a cat are shown. During the beginning of the convulsion, as already mentioned, a transient inhibition of the flow of blood through the submaxillary gland can be seen. The rise of blood pressure during the muscular contraction is prominent in this figure.

In *B* the effect of thujone and histamine is recorded. The increase in respiratory rate, the fall of blood pressure and the vasodilatation are marked. During the few jerks that took place only a slight irregularity in the flow of blood through the submaxillary gland occurred, the pial artery remaining dilated throughout.

In *C* the record of status epilepticus has been made. This appeared in a cat after a large amount of thujone had been injected in fractional doses. Each of the brief jerks at regular intervals is seen to be accompanied by a slight rise of blood pressure and increased aeration. After 0.5 mg. of acetylcholine the convulsions completely disappeared for a time, while the flow of blood through the gland and the size of the pial artery remained practically unaltered.

TABLE 1.—*Rabbits Given Sympathetic Activating Drugs Intravenously with One Half the Convulsant Dose of Thujone*

Substance	Dosage, Mg. per Animal	Animals Used	Number With Convulsions	Number Without Convulsions	Percentage With Convulsions
Epinephrine*	0.1 cc. 1:1,000	6	5	1	83
Pitressin*	0.1 cc.	6	5	1	83
Nicotine	0.5	6	6	0	100
Histamine	0.5	10	8	2	80
Beta-tetra-hydronaphthylamine	3-10 (per Kg.)	12	3	9	25
Ephedrine	20	4	0	4	0
Controls	..	26	5	21	19.2

* Keith.[44]

Effects of Sympathetic Stimulants (Nicotine, Histamine, Beta-Tetrahydronaphthylamine, Ephedrine).—As already stated, a marked increase in susceptibility to convulsions can be brought about by the addition of epinephrine or pitressin to the thujone. It seemed interesting to note whether other sympathetic stimulants would have any such influence. It is well known that nicotine in small doses activates the sympathetic nervous system. Accordingly 0.5 mg. of nicotine was administered to each of six rabbits with one half of the convulsant dose of thujone. All six had definite convulsions (table 1).

A second drug, placed in the same group, was histamine. Although this substance is believed to have an amphoteric action on the autonomic nervous system, Barger and Dale [47] have shown that the uterine muscle reacts to it as to hypophyseal extracts, by contraction.

47. Barger, G., and Dale, H. H.: B-Iminazolylethylamine, a Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1910-1911.

MacKay [48] and Stavraky [49] have demonstrated in the instance of the salivary gland that histamine excites the contractile elements, which have been found to be under the control of the sympathetic nerves (Stavraky [50]). Also in the instance of the pancreatic secretion (Popielski,[51] MacKay [48]) and other examples the effect of histamine differs from that of stimulation of the parasympathetic nerves. As in the experiment cited, 0.5 mg. of histamine phosphate was given to each of ten rabbits with one half of the convulsant dose of thujone. Eight of the ten (80 per cent) responded at once with definite attacks (see table 1). In cats, also, histamine appeared to augment the effect of thujone to some extent, but its action was not so pronounced as in the rabbit.

As a further example of sympathetic stimulants beta-tetra-hydronaphthylamine hydrochloride has been employed. This drug was used in amounts of from 1 to 10 mg. per kilogram of body weight, followed in from one to three minutes by one half of the convulsant dose of thujone. In spite of a pronounced peripheral vasoconstrictor effect, as judged by the blanching of the rabbit's ears, it did not cause any definite increase in the animal's response to thujone; i. e., of the twelve animals treated in this way, only three (25 per cent) had moderate convulsions.

Ephedrine, another example of an artificial sympathetic stimulant, was used in a similar way. As was pointed out by Keith, when administered in amounts of 10 mg. per rabbit with or shortly before the thujone, ephedrine sulphate has no augmenting effect on the rabbits' susceptibility to convulsions. This has been confirmed in the present investigation; even when the ephedrine was repeated in thirty minutes and the thujone was given after one hour, to allow the full action of ephedrine to develop, no increase in the rabbits' susceptibility to convulsions occurred.

Effects of Parasympathetic Stimulants (Acetylcholine, Acetyl-Beta-Metheyl-Choline, Choline, Pilocarpine, Physostigmine).—In contradistinction to some of the sympathomimetic agents, the following parasympathetic stimulants have been used: acetylcholine bromide, acetyl-beta-methyl-choline chloride, choline hydrobromide, pilocarpine hydrochloride and physostigmine hydrochloride.

48. MacKay, Margaret E.: Histamine and Salivary Secretion, Am. J. Physiol. **82**:546, 1927; Further Data Concerning Histamine Salivary Secretion, ibid. **91**: 123, 1929.

49. Stavraky, G. W.: The Response of the Submaxillary and Parotid Glands of the Dog to Histamine, J. Pharmacol. & Exper. Therap. **43**:265 (Oct.) 1931.

50. Stavraky, G. W.: The Effect on the Submaxillary Gland of Stimulation of the Partly Degenerated Sympathetic Nerve, Quart. J. Exper. Physiol. **21**:123 (Aug.) 1931.

51. Popielski, L.: B-Imidazolyläthylamin und die Organextrakte, Arch. f. d. ges. Physiol. **178**:214, 1920.

Each of seventeen rabbits (weighing from 1.5 to 2 Kg.) was given 0.3 mg. of acetylcholine combined with one full convulsant dose of thujone. The latter was first measured in a syringe and the former was drawn into the same syringe immediately before injection. As is seen in table 2, fourteen (82 per cent) of the rabbits did not have any convulsion and three had minimal attacks. This effect of acetylcholine disappeared rapidly, since each of four rabbits, in which the interval between the injection of the drugs was three minutes, had a definite convulsion. The preceding experiment was repeated in previously atropinized animals, and the inhibitory effect of acetylcholine on the convulsions was found to be almost completely absent. Of eight rabbits treated in this way, six (75 per cent) had moderate or severe convulsions, the remaining two (25 per cent) having no definite attack (table 2).

TABLE 2.—*Rabbits Given Parasympathetic Activating Drugs Intravenously with One Full Convulsant Dose of Thujone*

Substance	Dosage, Mg. per Animal	Animals Used	Number With Convulsions	Number Without Convulsions	Percentage Without Convulsions
Acetylcholine	0.3	17	3	14	82.4
Atropine	6.0)*	8	6	2	25
Acetylcholine	0.3)*				
Acetyl-beta-methylcholine	0.1-0.3	17	9 (slight convulsion)	8	47
Choline	50-200	9	8	1	11
Pilocarpine	3.0	7	5	2	28
Physostigmine	1.0	18	13	5	28
Controls	..	7	7	0	0

* These two given together.

An inhibitory effect similar to that of acetylcholine, although not quite so pronounced, was exhibited by acetyl-beta-methyl-choline. Each of seventeen rabbits was given from 0.1 to 0.3 mg. of this drug with the full convulsant dose of thujone. Eight of these had no thujone effect whatever, six had twitching of the head and ears only, while the remaining three had definite moderate convulsions (table 2).

In unanesthetized cats this effect of acetylcholine and acetyl-beta-methyl-choline could not be readily demonstrated. Each of these substances, when used in amounts sufficient to prevent the thujone fits, produced peculiar vermiform movements, suggestive of athetoid movements, which sometimes ended in a brief state of tonus resembling a transient decerebrate rigidity.

In rabbits, acetylcholine alone also produces these movements, but when balanced with a certain amount of thujone the two drugs seemed to counteract one another to such an extent that the animal was left completely free from any motor phenomena. In anesthetized cats, however, the inhibitory effect of acetylcholine on convulsions could be seen clearly. An example of this effect may be observed in figure 2 *C*.

It is interesting that this inhibitory effect seems to be limited to the acetylcholine and acetyl-beta-methyl-choline (table 2). Choline itself had no such effect. Also no marked inhibitory effect on the convulsions was exhibited by pilocarpine or physostigmine (table 2). In the literature there are indications that physostigmine administered to the epileptic patient (Cushny [52]) tends to increase the number of attacks. This could not be observed in thujone convulsions. On the contrary, as is seen in table 2, there was some decrease in convulsability, since five of eighteen rabbits treated with physostigmine did not have convulsions although given the full convulsant dose of thujone.

Effects of Sympathetic Paralyzing Drugs (Ergotamine, Nicotine).—Of the sympathetic paralyzing agents, ergotamine and nicotine were employed. Both ergotamine tartrate and methane sulphonate were used. Altogether eleven rabbits were given different amounts varying from 2 to 7 mg. per kilogram of body weight. Of the eight animals given from 5 to 7 mg. per kilogram of either salt, three had convulsions and five had no definite thujone effect. In three rabbits given smaller amounts of ergotamine (from 2 to 4 mg. per kilogram) there developed slight convulsions only. In three cats ergotamine (from 2.5 to 3.5 mg. per kilogram) did not prevent the thujone convulsions. It is worth noting that after the injection of ergotamine and thujone all the animals died within twenty-four hours, although either drug given alone did not appear to be lethal (table 3).

Twelve cats and six rabbits were used in the experiments with nicotine. The latter was given in gradually increasing fractional doses over periods varying from one to two hours, in amounts totaling from 12 to 45 mg. per animal. The amount necessary to produce any one effect differed greatly in the individual animal. The first few injections were given intraperitoneally, the final injections intravenously. The animals, at first excited and vomiting, gradually became dull, the pupillary reaction disappeared, and if the injections were continued an ascending paralysis occurred, beginning in the hindlimbs and spreading to the forelimbs and neck, but almost invariably leaving the facial and respiratory muscles intact to the last. In different stages the cats were given a full dose of thujone, without any definite relation being found between the susceptibility to convulsions and the extent of the depression.

As examples of this variability of response of the nicotinized animals to thujone, two abstracts of protocols may be quoted:

1. Cat 333.—The weight was 3.1 Kg. The dose of nicotine was 30 mg. There was no reaction of the pupils to light. The cat was able to walk about. The full dose of thujone did not cause a convulsion.

52. Cushny, A. R.: A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease, ed. 7, Philadelphia, Lea & Febiger, 1918, p. 349.

2. Cat 332.—The weight was 1.9 Kg. The dose of nicotine was 15 mg. There was no reaction of the pupils to light; there was complete paralysis of voluntary movements of the extremities. The cat was lying on its side, breathing regularly, licking its lips and swallowing. The full dose of thujone caused no perceptible change in the size of the pupils, but did cause jerking of the ears and of the muscles of the face, and accelerated the respirations—a modified convulsion.

These examples demonstrate, in our opinion, that the state of depression of the somatic nervous system which occurs after nicotine poisoning modifies but does not necessarily prevent the attacks.

It also seems that the paralysis of the autonomic nervous system—as judged by the absence of reaction of the pupils to light and the absence of micturition, defecation, erection of the hair, etc., on administration of thujone—is not a decisive factor, and that some other more specific conditions are probably responsible for the absence or the occurrence of convulsions in the animals treated with nicotine.

Table 3.—*Rabbits and Cats Given Sympathetic Paralyzing Drugs with One Full Convulsant Dose of Thujone*

Drug	Animals Used	Amount of Drug, Mg. per Animal	Number With Convulsions	Number Without Convulsions	Percentage Without Convulsions
Nicotine	6 rabbits	20-30	3	3	50
	12 cats	12-45	6	6	50
Ergotamine	8 rabbits	8-10	3	5	62.5
	3 rabbits	5-7	3	0	All slight convulsion
	3 cats	6-8	3	0	All slight convulsion

In spite of this variability, if the whole group of such animals is regarded statistically, it is apparent (table 3) that in 50 per cent of the animals nicotine prevented the thujone convulsions.

In the rabbits nicotine had much the same effect, but in the more advanced states of its action the depression of motor activity was much less pronounced.

Effect of Parasympathetic Paralyzing Drugs (Atropine, Hyoscyamine, Scopolamine.)—Of the parasympathetic paralyzing agents, atropine sulphate, hyoscyamine sulphate and scopolamine hydrobromide have been studied. As noted in table 4, ten rabbits were each given 8 mg. of atropine sulphate intravenously. Two minutes later, six of them were given a full convulsant dose of thujone and four only one half of the convulsant dose. All of the first six had rather severe convulsions, but none of the remaining four had any thujone effect. Hyoscyamine and scopolamine used in the same way could not be shown to have any definite effect.

COMMENT

It has been pointed out by MacDonald and Cobb [53] and by Pike, Elsberg, McCulloch and Chappell [54] that in convulsions caused by the administration of absinth a transient blanching of the pial blood vessels may take place. On the other hand, an increased flow of blood through the cerebral vessels during absinth and thujone convulsions has been reported by Hill and Nabarro,[55] d'Ormea,[56] Florey,[5] Gibbs [57] and others. Magnan [58] reported dilatation of the vessels of the fundus during absinth convulsions.

Studying the eyegrounds of rabbits during thujone convulsions, we occasionally could see distinctly a transient blanching of the vessels of the retina at the beginning of the convulsion. This effect not being constant, however, and also dilatation of the retinal blood vessels having been observed, it seemed interesting to check the observation by some more exact method.

For this purpose the flow of blood through the submaxillary salivary gland in cats under dial anesthesia was taken as an indicator of the

TABLE 4.—*Rabbits Given Parasympathetic Paralyzing Drugs and Thujone*

Drug	Animals Used	Amount of Drug, Mg. per Animal	Amount of Thujone	Number With Convulsions	Number Without Convulsions	Percentage Without Convulsions
Atropine	6	8	1 c.d.*	6	0	100
	4	8	½ c.d.	0	4	0
Hyoscyamine	4	8	1 c.d.	4	0	100
Scopolamine	4	8	1 c.d.	4	0	100

* 1 c.d. means full convulsant dose; ½ c.d., one-half convulsant dose.

circulatory changes occurring in a visceral organ during a thujone convulsion, and readings of the diameter of the pial arteries were made simultaneously. By counting the drops of blood from the submaxillary vein the total amount of blood passing through the gland could be determined. As the capsule of the gland was opened in every case and

53. MacDonald, M. E., and Cobb, S.: Intracranial Pressure Changes During Experimental Convulsions, J. Neurol. & Psychopath. **4**:228, 1923.

54. Pike, F. H.; Elsberg, C. A.; McCulloch, W. S., and Chappell, M. N.: The Problem of Localization in Experimentally Induced Convulsions, Arch. Neurol. & Psychiat. **23**:847 (May) 1930.

55. Hill, L., and Nabarro, D. N.: On the Exchange of Blood-Gases in Brain and Muscle During States of Rest and Activity, J. Physiol. **18**:218, 1895.

56. d'Ormea, A.: Sur les modifications de la circulation cérébrale à la suite de l'administration de quelques essences, Arch. ital. di biol. **40**:141, 1903.

57. Gibbs, F. A.: Cerebral Blood Flow Preceding and Accompanying Experimental Convulsions, Arch. Neurol. & Psychiat. **30**:1003 (Nov.) 1933.

58. Magnan, V.: Recherches sur les centres nerveux, Paris, G. Masson, 1876.

the muscular branches of the vein tied off, the convulsion itself could not have had any marked effect on the volume of blood passing through the organ. The changes in the pial vessels coincided closely with the vascular changes in the gland.

As observed in the tracings, subminimal and medium doses of 1 per cent thujone (fig. 1 *A* and *B*) under the conditions of our experiments usually caused dilatation of the pial artery and a coincident increase in the flow of blood through the submaxillary gland, the fall of the systemic blood pressure showing that this vasodilatation was widespread. On some occasions this increased circulation immediately before the convulsion was inhibited and a transient decrease of the circulation in the submaxillary gland could be seen (fig. 1 *B* and 2 *A*). This inhibition was more marked on the addition of epinephrine to the thujone and was so transient that the total amount of blood passing through the organ in a given time was not much decreased, and chiefly an irregularity of the blood flow occurred. However, on two occasions when a large sublethal dose of the drug had been given to a cat after several previous injections of thujone and epinephrine hydrochloride, the convulsions took place during a diminished flow of blood through the salivary gland, the pial artery remaining almost unchanged. It is interesting that in these cases, also, a depression of the respiration took place instead of the usual increase.

This seems to indicate that, depending on the sensitivity of the animal and the dose of thujone, it is possible to obtain a convulsion with a preceding increase in the circulation in different organs and also with a decrease in the same. The convulsion may also occur with an increase or a decrease of the respiration.

This conclusion is analogous to the latest observations of Finesinger and Cobb.[59] These investigators in a careful study of the blood pressure, cerebrospinal fluid pressure and diameter of the pial artery during experimental convulsions also found that the convulsion brought about by the administration of absinth can be preceded either by a decrease or an increase of the size of the pial arteries. It is true that in their experience smaller doses of the oil of absinth produced a diminution and larger doses a dilatation of the arteries, whereas in the present observations the relation of the size of the arteries to the dosage of thujone seems to be reversed. However, if the differences in technic are considered this discrepancy may probably be accounted for. Finesinger and Cobb [59] used light ether and morphine anesthesia and oil of absinth as a convulsant, whereas most of the present observations have

59. Finesinger, J. E., and Cobb, Stanley: Cerebral Circulation: XXVII. Action on the Pial Arteries of the Convulsants Caffeine, Absinth, Camphor and Picrotoxin, Arch. Neurol. & Psychiat. **30**:980 (Nov.) 1933.

been carried out under dial anesthesia (barbituric acid derivatives are known to alter many a vascular reaction as shown by Eddy,[60] Lieb and Mulinos,[61] Shafer, Underwood and Gaynor,[62] Garry,[63] Ross and Stehle,[64] Raginsky, Ross and Stehle,[65] Ross, Dreyer and Stehle,[66] Goldenberg and Rothberger,[67] Stavraky,[68] Raginsky and Stehle[69] and others) and thujone has been used as the convulsant agent. The dose of this convulsant under dial anesthesia had also been larger than is necessary in unanesthetized animals. It may be that the constriction of the retinal blood vessels which we observed in unanesthetized rabbits with a minimal convulsant dose corresponds to that reported by Finesinger and Cobb[59] with small doses. The medium doses of thujone which we used in cats correspond to their larger doses. In that case our last sublethal doses can be regarded as true depressing doses of the drug and are probably larger than any dose used by Finesinger and Cobb.[59]

Pike and his co-workers expressed the opinion that most of the drugs which raise the systemic blood pressure facilitate the production of convulsions and vice versa. In the majority of cases this really seems to be so, but it does not hold true in every case Thus histamine, although it lowers the blood pressure, increases the susceptibility of the animals to thujone convulsions, whereas beta-tetra-hydronaphthylamine, in spite of the marked peripheral vasoconstriction and rise of blood pressure, does not influence the convulsive state to any extent.

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60. Eddy, N. B.: Studies on Hypnotics of Barbituric Acid Series, J. Pharmacol. & Exper. Therap. **33**:43, 1928.

61. Lieb, C. C., and Mulinos, M. G.: Some Further Observations on Sodium Iso-Amyl-Ethyl-Barbiturate as Laboratory Anesthetic, Proc. Soc. Exper. Biol. & Med. **26**:709, 1929.

62. Shafer, G. D.; Underwood, F. J., and Gaynor, E. P.: Action of Amytal in Impairing Vagus Cardiac Inhibitory Effects, and of Ether in Increasing the Respiratory Rate After Its Depression by Amytal, Am. J. Physiol. **91**:461, 1930.

63. Garry, R. C.: Some Observations on Suitability of Amytal as Anesthetic for Laboratory Animals, J. Pharmacol. & Exper. Therap. **39**:129, 1930.

64. Ross, J. B., and Stehle, R. L.: Cardiac Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **38**:451, 1930.

65. Raginsky, B. B.; Ross, J. B., and Stehle, R. L.: Action of Pituitary Extract upon Blood Pressure, J. Pharmacol. & Exper. Therap. **38**:473, 1930.

66. Ross, J. B.; Dreyer, N. B., and Stehle, R. L.: Cardiac Action of Pituitary Extract (Posterior Lobe), J. Pharmacol. & Exper. Therap. **38**:467, 1930.

67. Goldenberg, M., and Rothberger, C. J.: Experimentelle Beiträge zur Theorie der Angina pectoris; Pitressinversuche, Ztschr. f. d. ges. exper. Med. **76**:1, 1931.

68. Stavraky, G. W.: Effect of Amytal on Autonomic Nervous System as Indicated by Salivary Glands, J. Pharmacol. & Exper. Therap. **43**:499, 1931.

69. Raginsky, B. B., and Stehle, R. L.: Influence of Sodium Phenobarbital (Sodium Luminal) on Cardiac Action of Pituitary Extract, J. Pharmacol. & Exper. Therap. **44**:385, 1932.

It should be noted that in rabbits in which histamine caused no significant fall in blood pressure (this being true of the whole group of herbivorous animals) thujone also did not influence it to the same extent as in cats, dogs and monkeys.

When histamine and thujone were administered together to rabbits, occasionally a transient rise of blood pressure preceded the convulsion, while during the latter the blood pressure was somewhat lowered. However, if a second convulsion occurred, the effect of histamine on the blood pressure having already subsided, this convulsion could be accompanied by a marked rise of blood pressure.

Testing systematically the different groups of pharmacologic agents which are known to have an effect on the autonomic nervous system, we have found that, generally speaking, the peripherally acting sympathetic stimulants seem to increase the liability of the animals to convulsions, and that the parasympathetic stimulants have the opposite effect. Thus substances which belong to the group of sympathetic hormones or drugs, such as epinephrine, pitressin and minimal doses of nicotine as well as histamine, markedly increased the susceptibility of our animals to convulsions, whereas acetylcholine and acetyl-beta-methyl-choline and, to a much less degree, pilocarpine and physostigmine had the reverse effect.

The more the substance used resembled an element which acts normally within the body, the more pronounced was its effect in either direction on the convulsions. Thus epinephrine, pitressin and acetylcholine were extremely active, whereas ephedrine and pilocarpine had little effect. Choline, an inert substance, had no pronounced effect even when used in large amounts and could not be compared in effect with acetylcholine.

Central stimulants such as beta-tetra-hydronaphthylamine and physostigmine also had little effect, and it appears that the peripherally acting physiologic stimulants of the autonomic nervous system are the only ones that have a pronounced effect on the liability of the animals to convulsions.

Drugs which have a depressing effect on the autonomic nervous system were found as a group to be comparatively inert. Atropine, hyoscyamine and scopolamine had little effect on the convulsions. Slightly more active were paralyzing doses of nicotine and ergotamine, which decreased the convulsions in 50 per cent of the animals. Since seizures could be brought about by thujone after atropine, ergotamine and nicotine poisoning it seems legitimate to assume that a convulsion can take place regardless of paralysis of autonomic innervation, this coinciding with the conclusion of Wortis.[70] However, it is impossible

70. Wortis, S. B.: Experimental Convulsive Seizures, J. Nerv. & Ment. Dis. **77**:233, 1933.

completely to exclude the participation of the autonomic nervous system in the convulsions brought about by thujone.

Besides its central action thujone may influence also some peripheral mechanisms which are not affected by the block. It is possible also to conceive that the doses of the paralyzing drugs have not been sufficiently large to abolish the effect of the autonomic nervous system altogether. The amounts of ergotamine and nicotine necessary to secure an inhibitory effect on the convulsions were quite large, and it is difficult to judge whether the effect was due to a specific paralysis of the peripheral sympathetic mechanisms or to the action of these drugs on the somatic nervous system. This is particularly true of nicotine, as this drug is considered to have a pronounced effect on the whole central nervous system, exciting the motor cells in small amounts and paralyzing them when applied in larger quantities (Frohlich [31]). A curara-like action of nicotine on the motor nerve endings in the striated muscles has been described (Langley and Dickinson [41]), an effect to which may be attributed also, to some extent, the motor paralysis observed in nicotine-poisoned animals during the present experiments.

In one type of experiment, however, the effect of the paralyzing agent was definitely specific. In experiments with acetylcholine, when the latter was given to rabbits with the thujone, the convulsions did not occur. If the animals had been previously atropinized the convulsions took place in spite of the presence of acetylcholine in the thujone suspension.

SUMMARY

1. (*a*) In cats under dial anesthesia the convulsions brought about by minimal convulsant doses of thujone are preceded by a general vasodilatation as judged by the fall in blood pressure, the increase in the size of the pial arteries and the increased flow of blood through the submaxillary salivary gland, as well as by the increase in the rate and volume of the respirations.

(*b*) Sublethal doses of thujone can produce convulsions which may be accompanied by an inhibition of the flow of blood through the salivary gland and by a decrease in the size of the pial arteries. This effect seems to be more marked after a preceding intravenous administration of epinephrine hydrochloride. The respiratory movements are also inhibited during this convulsion and not increased as with the smaller doses of thujone.

2. Sympathetic stimulants, such as epinephrine and pitressin, and small doses of nicotine, as well as histamine, when added to the thujone, markedly increase the severity of the convulsions and lower the minimal convulsant dose of the drug itself in unanesthetized cats and rabbits.

3. Stimulants of the parasympathetic nervous system, such as acetylcholine, acetyl-beta-methyl-choline and, to a much less degree, pilocarpine and physostigmine, when added to the thujone, tend to prevent the occurrence of convulsions. This effect of the parasympathomimetic drugs is abolished by atropine, a preceding injection of which renders the animals susceptible to convulsions in spite of the presence of acetylcholine, for example, in the thujone.

4. Nicotine and ergotamine administered in doses which depress the sympathetic nervous system prevented the occurrence of thujone convulsions in 50 per cent of the animals.

5. Atropine, scopolamine and hyoscyamine administered in physiologic amounts had little effect on thujone convulsions.

6. Other drugs reported to affect the autonomic nervous system, such as beta-tetra-hydronaphthylamine, ephedrine and choline, did not alter noticeably the susceptibility of the animals to convulsions.

VISCERAL AND REFERRED PAIN

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CHICAGO

The term "visceral pain" usually is restricted to pain that occurs in, or is produced by, changes in the state of intrathoracic, intra-abdominal or intrapelvic organs. Referred pain from the viscera, according to the generalizations of Head, is characterized, in part, as often being remote from the site of irritation, following the lines of spinal segmentation on the skin rather than the course of peripheral nerves, and usually being associated with cutaneous hyperesthesia.

Soon after the development of the operation of colostomy it was observed that the colon is insensitive to cutting, pricking or burning. To explain this, Lennander [1] assumed that the abdominal viscera are entirely devoid of sensory nerves capable of producing pain and that all painful sensations from disease of intraperitoneal organs originate in the parietal peritoneum and its subserosal layer, which is richly supplied with cerebrospinal sensory nerves. This idea was definitely disproved by Neumann [2] and Kast and Meltzer.[3] A few years earlier Ross [4] set forth his view that there are two kinds of pain in the disease of internal organs: (1) a true splanchnic pain which is felt in the organ and (2) an associated somatic pain which is felt in that part of the body wall which is connected by cerebrospinal nerves with the same segments of the cord as the affected splanchnic nerves. In respect to the associated somatic pain he said:

> . . . when the splanchnic peripheral terminations of the fourth, fifth and sixth thoracic nerves are irritated, the irritation is conducted to the posterior roots

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Read before the Association for Research in Nervous and Mental Disease, Dec. 27, 1934.

From the Department of Nervous and Mental Diseases and the Department of Surgery, Northwestern University Medical School.

1. Lennander, K. B.: Ueber die Sensibilität der Bauchhöhle und über lokale und allgemeine Anästhesie bei Bruch und Bauchoperationen, Zentralbl. f. Chir. **28**:200, 1901.

2. Neumann, A.: Zur Frage der Sensibilität der inneren Organe, Zentralbl. f. Physiol. **24**:1213, 1910-1911.

3. Kast, L., and Meltzer, S. J.: Die Sensibilität der Bauchorgane, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **19**:586, 1909.

4. Ross, J.: On the Segmental Distribution of Sensory Disorders, Brain **10**:33, 1888.

of the nerves, and on reaching the gray matter of the posterior horns it diffuses to the roots of the corresponding somatic nerves and this causes an associated pain in the territory of distribution of these nerves which may appropriately be named the somatic pain.

Although this theory of referred pain is ordinarily attributed to Ross, Lange [5] stated long before that all pain in visceral disease is of purely reflex origin. Mackenzie [6] was much impressed with the significance of Ross' somatic, or referred, pain but was doubtful of the existence of splanchnic pain since he believed that it also is referred. Although Mackenzie believed that the viscera are supplied with afferent splanchnic fibers, he did not believe that visceral painful impulses transmitted through these nerves to the central nervous system reach consciousness. He found areas of cutaneous hyperalgesia in cases of visceral disease and contraction of the muscles of the abdominal wall due to disease of an abdominal organ. From these observations he described the symptoms of pain and hyperalgesia in consequence of disease of the viscera as a "viscerosensory reflex" and the contraction of the muscles as a "visceromotor reflex." Head,[7] unlike Mackenzie, supported Ross' view of splanchnic or visceral pain. He believed that although visceral pain is for the most part referred there is, in addition, a low form of protopathic pain which represents true visceral sensation. From his study of a series of cases of herpes zoster he mapped out the somatic areas along which pain is referred in visceral disease. The view that the viscera themselves are insensitive to painful stimuli finally was refuted completely by Hurst,[8] who attached great importance to the work of Kast and Meltzer. Hurst pointed out that the viscera are sensitive only to appropriate stimuli, and, although they may be cut, pinched or burned without pain, increased tension on their muscular walls produces true visceral pain. It is now known that visceral afferent impulses may appear in consciousness as a painful sensation, and that at least in the stomach or intestines there is also a crude form of temperature sensibility.

The conception of a viscerosensory reflex as proposed by Mackenzie was attacked by Morley,[9] who had become convinced that true visceral pain exists and that it is usually the result of abdominal tension on the

5. Lange, C.: Nogle bemärkninger om neuralgier og deres behandling, Hospitalstid. **2**:641, 1875.

6. Mackenzie, J.: Symptoms and Their Interpretation, London, Shaw & Sons, Ltd., 1920.

7. Head, H.: On Disturbances of Sensation with Especial Reference to the Pain of Visceral Disease, Brain **16**:1, 1893; **17**:339, 1894; **19**:153, 1896.

8. Hurst, A. F.: The Sensibility of the Alimentary Canal, New York, Oxford University Press, 1911.

9. Morley, John: Abdominal Pain, New York, William Wood & Company, 1931.

walls of the hollow viscera. It is in no sense referred to the superficial structures of the abdominal wall and is a deep-seated, central pain not accurately localized. He believed that the phenomena of deep and superficial tenderness and muscular rigidity of the abdominal wall observed in association with inflammatory disorders in the abdomen are entirely referred from the highly sensitive cerebrospinal nerves to the parietal peritoneum. In this process two closely related mechanisms are concerned which he described as "peritoneocutaneous radiation" or the "peritoneomuscular reflex." In support of this theory, he referred to the shoulder tip pain of diaphragmatic origin as a striking example of referred pain. He said that in this instance there is no question of a viscerosensory reflex. He believed that the rest of the parietal peritoneum lining the abdominal wall resembles the peritoneum lining the diaphragm. It differs only in that each spinal segment which supplies nerves to a strip of parietal peritoneum also supplies a strip of overlying skin. The pain produced by stimulation of this parietal peritoneum is referred or radiates to the superficial structures exactly as in phrenic shoulder tip pain and is not appreciated as arising in the parietal peritoneum at all.

This conception was in turn attacked by Woolard, Roberts and Carmichael [10] and by Bolton.[11] The question whether referred pain originates only from the peritoneum or viscera is not particularly germane to our problem, and the literature concerning it will not be discussed further.

Interest in the question of the mechanism of this referred pain was stimulated further by the report of Daniélopolu and Hristide [12] of the cessation of anginal pain on injection of alcohol into the second and third intercostal nerves.

Impressed by this work, Lemaire [13] produced local anesthesia of the entire abdominal wall and later of only the subcutaneous tissues and observed disappearance of pain, tenderness and rigidity of the abdominal wall in patients suffering from various intra-abdominal diseases. From these observations he concluded that the visceral stimulus must be referred not through the spinal cord but through the bipolar cells of the posterior root ganglia. Weiss and Davis [14] anesthetized the

10. Woolard, H. H.; Roberts, J. E. H., and Carmichael, E. Arnold: An Inquiry into Referred Pain, Lancet **1**:337, 1932.

11. Bolton, Charles: Observations on Referred Pain, Brain **57**:211, 1934.

12. Daniélopolu, D., and Hristide, M.: Resection of Spinal Nerves in Angina Pectoris, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:69, 1923.

13. Lemaire, A.: La perception des douleurs viscérales, Rev. méd. de Louvain **6**:81, 1926; Recherches cliniques sur le mode de perception de douleurs viscérales, Bull. Acad. roy. de méd. de Belgique **6**:158, 1926.

14. Weiss, S., and Davis, O.: The Significance of Afferent Impulses from the Skin in the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517, 1928.

skin into which pain was referred in 25 patients suffering from various diseases, such as angina pectoris, pleuritis, carcinoma of the esophagus, gastric ulcer, cholecystitis, nephrolithiasis, acute appendicitis, salpingitis and pyelitis, with either complete relief from the pain or relief to a large extent. They also were able to prevent the occurrence of pain due to distention of the esophagus or duodenum by a balloon. They believed that this was added proof of the truth of Mackenzie's viscerosensory reflex. Morley, however, insisted that although these observations were correct they supported his theory of a peritoneocutaneous radiation rather than a viscerocutaneous reflex. He repeated these experiments in 13 patients suffering with acute abdominal lesions and was able to confirm Weiss and Davis' findings.

Since then numerous observers have confirmed these reports in part (Ferrari[15]). When a local anesthetic failed to relieve the pain of visceral disease it was thought that the pain was mediated through the corticospinal nervous system in accordance with Lennander's theory, and when it relieved pain the pain was due to a true visceral reflex mediated by the sympathetic afferent system.

The intimate relation of the skin to referred pain is seen in the observations by Mackenzie and Head of cutaneous hyperalgesia, in the reference of pain to areas of skin far removed from the site of irritation reported by Hilton,[16] Lange, Ross and others, and finally in the observations of Lemaire and others that in any instance in which pain is referred into a segment of skin it can be stopped by rendering this segment analgesic by injection of procaine hydrochloride and other agents and that such pain is diminished and at times stopped by local application of cold, heat, rubefacients and irritants.

Numerous theories have been evolved to explain the part played by the innervation of the skin. Lange believed that afferent impulses from the vegetative nervous system enter the spinal cord from which radiation occurs along the sensory nerves. Ross thought that the irritation is conducted through the posterior roots to the posterior horns where it diffuses to the roots of the corresponding somatic nerves. Mackenzie believed that a painful stimulus from a viscus passes up through the splanchnic afferent fibers to the spinal cord, then sets up, by radiation, an irritable focus and so by lowering the threshold produces cutaneous hyperalgesia in the skin of the abdominal wall supplied by the cerebrospinal sensory nerves that entered the affected segments of the spinal cord. In addition to calling attention to the possibility that the visceral afferent fibers of the sympathetic nervous system are

15. Ferrari, Roberto C.: Contribucion al estudio de las algias viscerales, Thesis, National University of Buenos Aires, no. 453, 1931.

16. Hilton, J.: Lectures on Rest and Pain, ed. 1, London, Bell & Daldy, 1863.

analogous to the protopathic system in the skin, Head supported the theory of reference of pain to some area on the surface of the body because the internal organs are devoid of epicritic sensibility and react, as does the skin, when epicritic sensibility is absent and protopathic present. Head stated:

> When a painful stimulus is applied to a part of low sensibility in close central connection with a part of higher sensibility the pain produced is felt in the part of higher sensibility rather than in the part of lower sensibility to which the stimulus was actually applied.

Spiegel [17] stated that the impulses produced by the irritation of the peripheral termination of the splanchnic nerves pass to the posterior horns and are there diffused to the roots of the corresponding somatic nerves, so that the pain and tenderness seem to occur in the territory of the distribution of these nerves.

Lemaire believed that the effect of subcutaneous anesthesia is to modify the excitability, throughout their whole extent, of the cerebrospinal neurons to which pain is referred and came to the conclusion that the visceral stimulus must be referred not through the spinal cord but through the bipolar cells of the posterior root ganglia. Morley said that he could not reject this conception.

Sicard [18] favored an inhibitory fiber from the skin to the anterolateral column with a synapse to the corticosensory system.

Verger [19] stated that the algogenic stimulus from the viscera produces a vasomotor reflex with a modification in the vascular bouquet of the skin which excites the sensory corpuscles, from which the impulses travel over the sensory cerebrospinal nerves through the posterior roots. He traced the impulse from the viscus by way of sympathetic afferent fibers through the posterior roots to the anterolateral column, and then by sympathetic efferent fibers running antidromically in the posterior roots to the skin. A sensory impulse from the skin is then conducted by way of the sensory cerebrospinal system.

A somewhat similar theory was proposed by Spameni and Lunedei,[20] who stated that the visceral impulses which reach the lateral columns of the cord by afferent pathways stimulate centrifugal unmyelinated

17. Spiegel, E.: Ueber das Wesen des Bauchschmerzes mit seinen Begleiterscheinungen, Wien. med. Wchnschr. **77**:379, 1927.

18. Sicard, J. A., and Lichtivitz, A.: Du rôle du derme dans le traitement des algies viscérales, Presse méd. **37**:545, 1929.

19. Verger, H.: Sur une modification du schème de Lemaire pour la conception physiologique de réflexe viscéro-sensitif de Mackenzie, Gaz. hebd. d. sc. méd. de Bordeaux **48**:419, 1927.

20. Spameni, P., and Lunedeir, A.: Sui reflessi viscero-cutanei e sul mecanismo di produzione del dolore nelle affezione dei visceri e delle sierose, Riv. di clin. med. **28**:758, 1927.

fibers which terminate in the sensory corpuscles. Physicochemical changes are thus produced which stimulate the sensory organs from which impulses travel over the cerebrospinal nerves.

Formerly we [21] attempted to study referred visceral pain by stimulation of the gallbladder by distention. We were unable to stop this pain by section of the intercostal nerves or anterior roots and concluded that we were producing a form of true splanchnic pain as well as referred pain, if the latter at all. We therefore sought for an experiment which would permit the isolation of referred pain. From the results of experiments and disease in man we believed that such a condition would be approached by stimulating the phrenic nerve.

Capps and Coleman [22] reported their results from stimulation of the diaphragmatic pleura by pressure and scratching with a wire, and concluded that sensation to the central portion of the diaphragm is supplied by the phrenic nerve and is referred to the neck region. They likewise concluded that stimulation of the central portion of the peritoneal diaphragm sets up pain over a sharply limited point along the trapezius ridge. These experimental observations have been amply confirmed by clinical observations by others. This, together with the fact that the shoulder tip pain due to disease of the viscera has been stopped by cutaneous analgesia by a number of observers, although Woolard, Roberts and Carmichael were not able to do so, led us to conduct a series of experiments on stimulation of the peritoneal surface of the diaphragm when various parts of the nervous system were severed.

TECHNIC

Under ether anesthesia, a small midline incision was made from the ensiform cartilage downward. A retractor was placed in the upper end of the incision, and a ribbon retractor protected by gauze was laid gently on the surface of the liver. This exposed the dome of the diaphragm and the central tendon. An insulated electrode in which the stimulating points were two small loops of platinum wire was sutured to the abdominal surface as near the midline as was possible. The insulated leads from the electrode encased in a rubber tube were brought out of the incision, and the latter was closed. Stimulation was effected by a Harvard inductorium with the secondary coils set at five or six.

The animal was allowed to recover from the ether until all superficial reflexes were brisk and it reacted easily to all noxious stimuli. A pneumograph was attached to the thoracic wall and connected with a writing tambour to record the respiratory movements. We do not subscribe to the view that the presence or absence of pain can always be recognized by respiration alone. After having studied a large number of animals we found that if, in addition, the animal was observed as a whole, the reaction to pain was as readily interpreted as in infants.

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21. Davis, Loyal; Pollock, Lewis J., and Stone, T. T.: Visceral Pain, Surg., Gynec. & Obst. **55**:418, 1932.

22. Capps, Joseph A., and Coleman, G. M.: Pain in the Pleura, Pericardium and Peritoneum, New York, The Macmillan Company, 1932.

Dilatation of the pupils, crying out, movements of the tail, unsheathing of the claws, erection of the vibrissae, facial expression and biting were noted in addition to striking and unmistakable changes in the respiratory rhythm in animals which had pain from stimulation of the diaphragm (fig. 1).

In animals in which the phrenic nerves were sectioned, these nerves were isolated in the neck, dissected free into the thorax and sectioned well down in the chest. A small laminectomy was performed at the desired levels for transection of the cord so that complete division of the cord could be accomplished under direct visual control. Sections of the posterior and anterior roots were all performed intradurally after an adequate laminectomy. The cervical sympathetic chains were removed, and by following the trunk downward into the thorax and

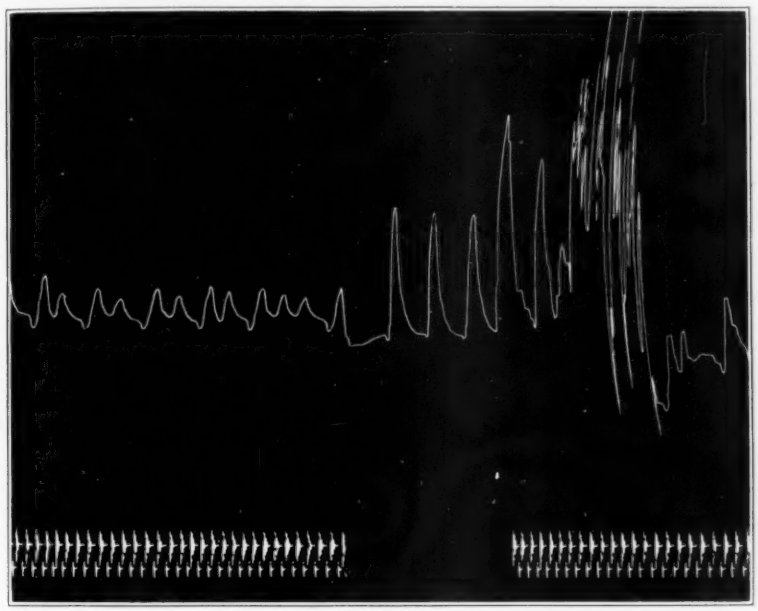

Fig. 1.—The posterior thoracic roots (fifth to twelfth, inclusive) were cut. A painful reaction is illustrated.

posterior to the pleura the stellate ganglion and a portion of the thoracic sympathetic trunk were easily removed.

RESULTS

Excluding many experiments in which drugs were combined with various anatomic sections and analgesia of the skin with anatomic sections, we find that good records were obtained with 135 different animals.

In 53 cases the operations performed were such as we later learned could not be expected to cause pain to disappear, such as section of the thoracic posterior roots; removal of one stellate ganglion or section of the splanchnic nerve; section of the phrenic nerves alone or combined with vagotomy; sections of the brachial plexus or intercostal nerves. The results in the remaining 82 animals lend themselves to analysis.

It was soon found that it was necessary either to cut the spinal cord at a level below the third thoracic segment or to section the thoracic posterior roots to obtain critical results by section of additional parts of the nervous system, as it was necessary to exclude the supply of the intercostal nerves to the periphery of the diaphragm because of spread of the current.

In earlier experiments the phrenic nerves were severed in the neck apparently too high up, and in 6 cases in which the thoracic posterior roots were severed and the phrenic nerves cut pain persisted. Later the phrenic nerves were cut within the thoracic cavity, and in 5 such cases no pain could be produced by stimulation of the diaphragm. In 7 cases of section of the spinal cord at the level of the fourth thoracic segment and of the phrenic nerves pain was stopped (fig. 2).

When the posterior roots of the cervical and thoracic segments of the spinal cord were severed pain was stopped in all of 4 cases. In 7 cases in which a sufficient number of posterior roots of the cervical region were severed, including

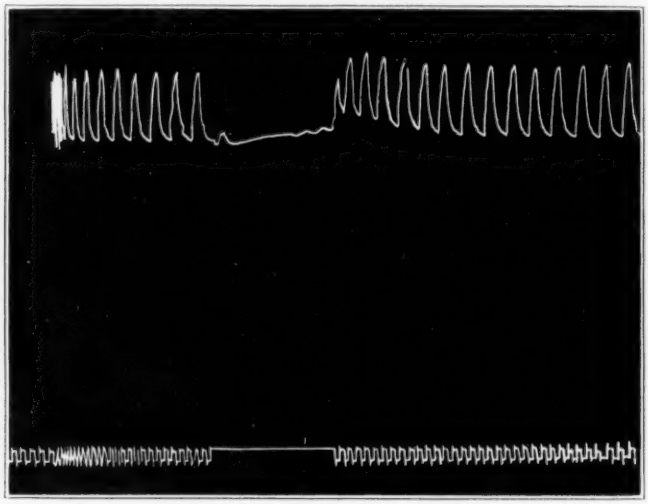

Fig. 2.—The phrenic nerves and thirteen posterior roots were cut bilaterally. No pain is shown.

the third cervical, pain was stopped, although the lower thoracic posterior roots were not severed. Here it is obvious that the electrodes were centrally placed and no spread of current occurred (fig. 3).

When an insufficient number of the cervical posterior roots were severed (4) or when thoracic posterior roots alone were severed (14) pain persisted.

We were able to stop the pain by severing the spinal cord at the level of the seventh cervical segment in 3 cases, indicating an interruption of the descending connecting sensory fibers to lower levels of the spinal cord. Destruction of the cord at the level of the first to third thoracic segment stopped the pain in 3 cases (figs. 4 and 5).

Section of the eighth cervical and the first, second, third and fourth thoracic anterior roots stopped the pain in 5 cases, thereby interrupting the sympathetic efferent preganglionic fibers (fig. 6).

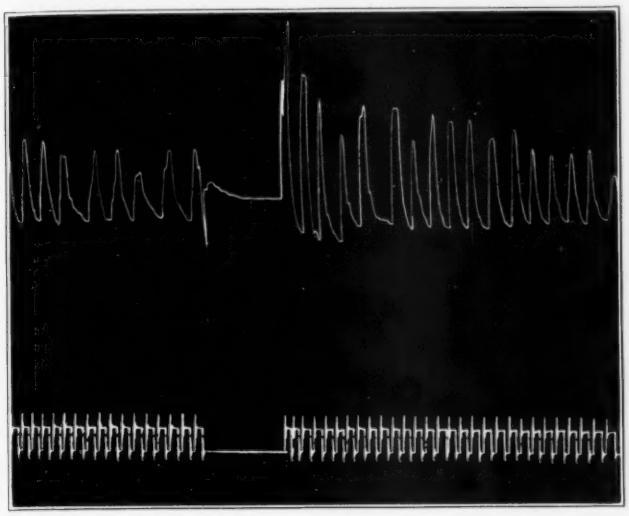

Fig. 3.—Seventeen posterior roots were cut bilaterally. No pain is shown.

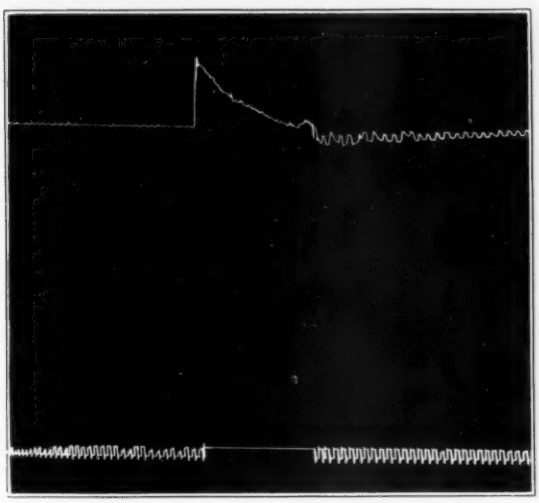

Fig. 4.—The spinal cord at the seventh cervical segment was sectioned. No pain is shown.

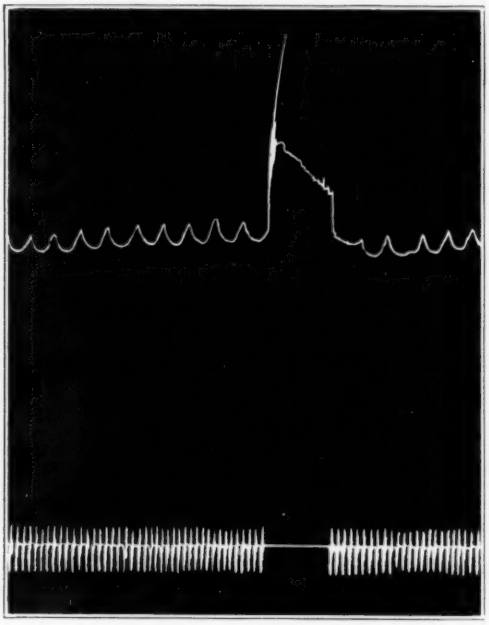

Fig. 5.—Destruction of the spinal cord at the second dorsal segment. No pain is shown.

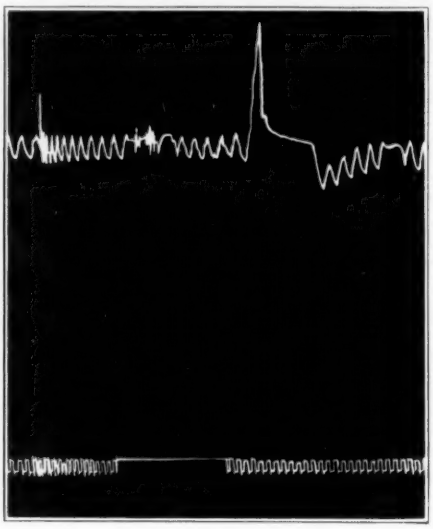

Fig. 6.—The eighth cervical root, the first, second and third anterior thoracic roots and the posterior thoracic roots were cut bilaterally. No pain is shown.

When the spinal cord was severed at the fourth thoracic segment to interrupt sensation from the intercostal nerves and the cervical sympathetic chains were removed bilaterally, pain was stopped in 9 cases, and when in 2 cases they were removed with section of the thoracic posterior roots pain was stopped. In 8 cases it was sufficient to remove only the stellate ganglia when the posterior thoracic roots were severed to stop pain, and in 3 cases when the spinal cord was severed and the stellate ganglia removed pain was stopped (fig. 7).

However, in 2 cases when the cord was severed and the stellate ganglia were removed pain persisted, and in 5 cases in which the stellate ganglia were removed and section of the thoracic posterior roots was done pain persisted. From the fact that when the sympathetic chain was removed with section either of the cord or of the thoracic posterior roots pain was always stopped it seems that in some cases in which the stellate ganglia alone were removed some connection with the cord remained intact.

We were unable to stop the pain by combined bilateral section of the brachial plexus and transverse lesion of the cord at the fourth thoracic segment in 4 cases.

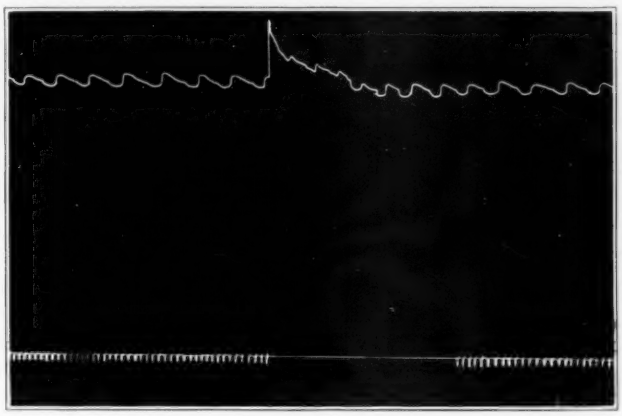

Fig. 7.—Bilateral section of the posterior thoracic roots and bilateral removal of the cervical sympathetic chains were performed. No pain is shown.

It must be remembered that we did not completely denervate the back by this procedure. Neither were we able to stop the pain by removing the entire skin of the upper extremities, neck and upper part of the chest. Other animals did not tolerate extensive subcutaneous analgesia, but the injection of procaine hydrochloride solution in these experiments was disappointing. Section of the cervical anterior roots, including the eighth cervical combined with section of the posterior roots of the thoracic region did not stop the pain, indicating that there was no antidromic sensory fiber or impulse traveling over the anterior root.

COMMENT

When the intercostal nerve supply is interrupted either by transection of the spinal cord or by section of a thoracic posterior root pain produced by stimulating the peritoneal diaphragm by the faradic current can be stopped by severing the phrenic nerve or removing the cervical

sympathetic chains; by severing the eighth cervical and the first, second and third dorsal anterior roots; by severing the cord at the seventh cervical segment; by destroying the cord at the first and second dorsal segments, and by severing the cervical posterior roots.

Afferent impulses travel over the phrenic nerve but do not directly ascend to a conscious level since the pain can be stopped by removing the sympathetic chains, the phrenic nerve being intact. That a connection is made between the level of the entrance of the phrenic nerve through the posterior cervical roots and the lower level of the cord at the eighth cervical and first, second and third dorsal segments is shown by the disappearance of pain when the cord is severed at the seventh cervical segment. From the cord at the level of the eighth cervical and first, second and third dorsal segments sympathetic efferent preganglionic fibers emerge to the cervical sympathetic ganglia; severance of these anterior roots stops the pain.

That painful impulses do not travel from the phrenic nerves directly over the sympathetic system by connection at the stellate ganglia is shown by the disappearance of pain when the eighth cervical and first, second, third and fourth anterior roots are severed.

Postganglionic fibers originate in the cervical ganglia, and removal of these stops the pain. They probably travel to the sensory endings of the skin, blood vessels and meninges and other structures. Although we were unable to stop pain by flaying or by sectioning the brachial plexus, anesthetizing the proper segment of the skin has in numerous instances stopped pain referred from visceral disease in man. From here the impulse travels along the cerebrospinal system, entering the cervical posterior roots, and reaches consciousness in the ordinary manner (fig. 8). These results are in keeping with those reported by us previously in relation to pain in the head.[23]

Without having read the work of Verger and Spameni and Lunedei we stated that stimulation of the superior cervical sympathetic ganglion produces an effect which is carried by way of postganglionic efferent fibers to structures innervated by sympathetic fibers. These efferent impulses produce an effect in the skin and other structures the exact nature of which we are unable to state. It is possible that it is linked with the sympathetic innervation of the blood vessels and that a metabolite is released which in turn stimulates the ordinary sensory nerve endings of the fifth nerve. This impulse is then transmitted centrally and is recognized as pain.

23. Davis, Loyal, and Pollock, Lewis J.: The Rôle of the Sympathetic Nervous System in the Production of Pain in the Head, Arch. Neurol. & Psychiat. **27**:282 (Feb.) 1932.

In this connection it is interesting to note the recent work of Windle [24] and O'Donnell and Windle [25] on sensory neurons in the ventral spinal roots. They described cells of sensory type in the ventral spinal nerve roots in man and other mammals. They suggested that these cells possibly "belong in the same category with those in the dorsal root ganglia

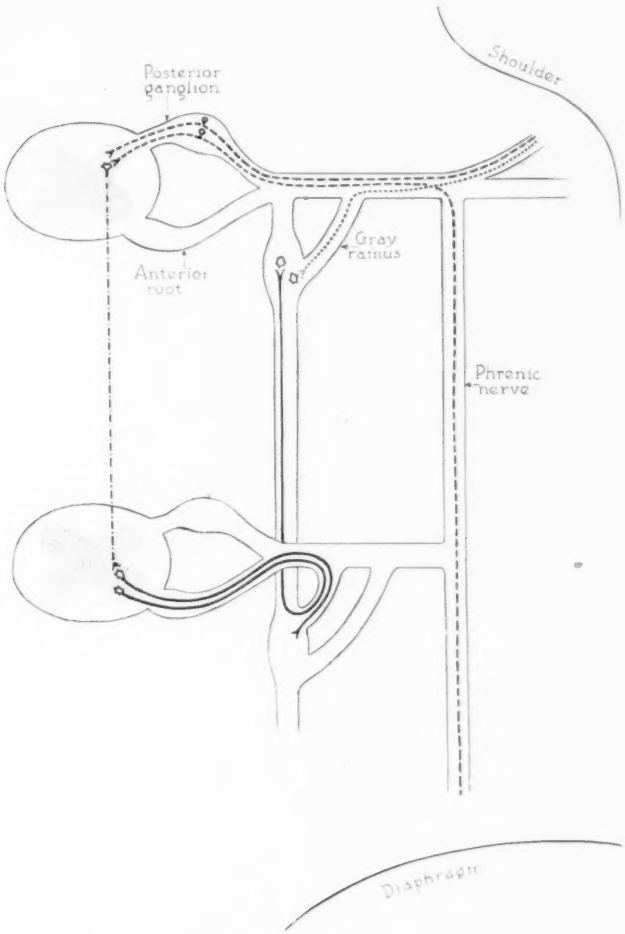

Fig. 8.—A diagrammatic representation of the theoretical mechanism for visceral referred pain.

24. Windle, William F.: Neurons of the Sensory Type in the Ventral Roots of Man and Other Mammals, Arch. Neurol. & Psychiat. **26**:791 (Oct.) 1931.

25. O'Donnell, Joseph E., and Windle, William F.: An Experimental Study of the Sensory Neurones in the Ventral Nerve Roots of the Cat, Anat. Rec. **55**:117, 1933.

which send 'recurrent' fibers into the ventral roots." They said: "It is somewhat speculative to suggest that these central fibers may reach the spinal cord by the dorsal roots and the peripheral ones pass to the meninges."

There is a possibility that these neurons, by supplying the vessels, meninges and roots, may be utilized in the mechanism of referred pain along with those supplying sensation to cutaneous and subcutaneous tissue.

CONCLUSIONS

The pain produced by faradic stimulation of the peritoneal diaphragm travels over the phrenic nerve; entering the cord by way of the posterior roots, it descends to the level of the eighth cervical and first, second and third thoracic segments; then a connection is made with cells in the intermediolateral column, and sympathetic efferent impulses travel over the preganglionic fibers through the anterior roots to the cervical sympathetic ganglia. From here postganglionic fibers travel to the skin, blood vessels, meninges and other structures, where by some vasomotor (?) or hormonal (?) process the sensory endings of the cerebrospinal system are stimulated and a sensory impulse travels over the ordinary cerebrospinal system, enters the spinal cord through the posterior roots and ascends to consciousness.

25 East Washington Street.

54 East Erie Street.

REMOVAL OF LEFT CEREBRAL HEMISPHERE

REPORT OF A CASE

ROBERT ZOLLINGER, M.D.
BOSTON

The right cerebral hemisphere has been removed in a few patients in order to extirpate completely a large glioma.[1] The following observations were made on a right-handed woman after the removal of the left cerebral hemisphere because of extensive infiltration by a tumor.

REPORT OF CASE

History.—Mrs. A. C., a white woman aged 43, was first admitted to the surgical service of the Peter Bent Brigham Hospital on June 22, 1933. For the preceding two weeks she had complained of heaviness and numbness of the right foot when walking. This disability followed an attack of vertigo, and the symptoms had become more severe after a second attack of vertigo.

Coldness over the dorsum of the right foot and absence of pulsations in the right dorsalis pedis artery were found by physical examination. Neurologic examination gave negative results. On entry the blood pressure was 170 mm. of mercury systolic and 100 mm. diastolic. Readings of skin temperature after immersion of the arms in hot water did not show the usual response over the dorsum of the right foot. A uniform rise in temperature, however, occurred over both extremities save over the dorsum of the right foot. The temperature of this localized area remained from 1 to 3 C. (from 1.8 to 5.4 F.) below that of the corresponding area on the left side. A diagnosis of thrombosis of the right anterior tibial artery and hypertension was made, and the patient was discharged from the hospital on June 27, 1933. One week after her discharge from the hospital there was a gradual onset of weakness of the right arm, which was accompanied by paralysis of the entire right side of the body. Attacks of nausea, vomiting, dizziness, headaches and occasionally dysarthria occurred, attended by emotional instability.

Because of these symptoms the patient was readmitted to the surgical service of the Peter Bent Brigham Hospital on July 28, 1933. At this time she was unable to cooperate with the examiner. She could not spell her name and gave the same answers to a series of questions. Physical examination showed the optic disks to be blurred at the nasal margin but without measurable choking. An accurate investigation of the perimetric fields of vision was impossible. A right hemiplegia was present.

First Operation.—Ventriculography was carried out on July 29, 1933. The ventriculograms showed both ventricles to be displaced considerably to the right,

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From the Surgical Service of the Peter Bent Brigham Hospital.

1. Dandy, W. E.: Physiological Studies Following Extirpation of the Right Cerebral Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31 (July) 1933. Gardner, W. J.: Removal of the Right Cerebral Hemisphere for Infiltrating Glioma: Report of a Case, J. A. M. A. **101**:823 (Sept. 9) 1933.

both anterior and posterior horns being equally displaced. The left lateral ventricle was displaced downward in its middle third, with a sharp concavity on its upper surface. The right ventricle was dilated but not deformed. These findings indicated a large postcentral tumor on the left side.

The patient's condition was so poor that subtemporal decompression on the left side was done immediately, with local anesthesia, and no attempt was made to remove the tumor. The condition remained unchanged for several weeks but gradually improved following intensive roentgen therapy. The patient was discharged slightly improved to Pondville, the state hospital for patients with cancer, on Sept. 30, 1933. The improvement was only temporary, and a gradual decline followed; she became drowsy and could be aroused only with difficulty.

The patient was transferred back to the Peter Bent Brigham Hospital for further surgical therapy on Nov. 16, 1933. She no longer knew her name and could not recognize relatives. Her vocabulary was limited to "bed, sleep, yes, no" and "all right," but these were not often used correctly.

Neurologic Examination on the Third Admission.—Cranial Nerves:

First Nerve. No disturbance on previous admissions.

Second Nerve. Vision was apparently fair. The perimetric fields were not examined. There was moderate choking of the optic disks.

Third, Fourth and Sixth Nerves. Extra-ocular movements were normal. The pupils were small but equal in size and regular; they reacted to light, but the patient did not cooperate well enough so that accommodation could be tested. There was no ptosis or exophthalmos.

Fifth Nerve. The corneal reflexes were active; the jaw opened without deviation.

Seventh Nerve. The right facial muscles were weak, especially to emotional grimaces.

Eighth Nerve. Hearing was apparently good on both sides. Dizziness had been present for two months, with a tendency to fall to the right.

Ninth Nerve. There had been dysarthria for one and one-half weeks. Tests for taste were not possible. The pharyngeal reflexes were moderately active.

Tenth Nerve. The pulse and respiration were normal. There were some regurgitation of fluids and difficulty of speech. There were nausea and nonprojectile vomiting of one week's duration.

Eleventh Nerve. No disturbance.

Twelfth Nerve. The patient was either unable or unwilling to protrude the tongue.

Motor and Sensory Changes: There was complete spastic paralysis of the right arm and leg. The right arm was held in adduction at the shoulder and the elbow flexed at 45 degrees. The fingers were slightly clinched, and the muscles of the hand exhibited fibrillary movements. The right triceps and biceps reflexes were hyperactive, and there was an active Hoffmann sign on the right. The right leg was extended, and the foot was held in extreme flexion. Ankle and patellar clonus (with Gordon, Oppenheim and Babinski signs) was present on the right and suggested on the left side. The right abdominal reflexes were absent. Painful stimuli were appreciated over the entire body, and any movement of the right arm, particularly the hand, caused considerable pain. This arm was held rigid at the shoulder and wrist but was freely movable at the elbow. The patient was incontinent both of feces and of urine. An inlying catheter, which had been in place for several months, was removed and a new one inserted.

Second Operation.—This was performed on Nov. 17, 1933. With the patient under satisfactory ether anesthesia, administered by the Connell method, a large flap of bone on the left was outlined, extending from just anterior to the hair line around to the occipital region. The flap was reflected and the dura opened. The area of brain in the decompression was bulging outward about 1 inch beyond the dura. There was no superficial evidence of tumor, but by palpation and needling a very large tumor was located just beneath the surface, apparently involving the middle third of the left hemisphere. The extirpation was begun by ligating the veins running from the middle of the hemisphere to the longitudinal sinus, using silk on the cerebral side and two silver clips on the side of the sinus. The flap of bone did not extend far enough forward to allow exploration beneath the frontal lobe and permit ligation of the necessary branches of the internal carotid artery. Several inches of the frontal bone were rongeured away. The hemisphere was retracted laterally, exposing the corpus callosum and permitting exposure of the left anterior cerebral and communicating arteries. These were doubly clipped, as was the middle cerebral artery. The lateral ventricle was then entered from the medial side above the corpus callosum and the hemisphere gradually removed from the basal ganglia (fig. 1). The floor and lateral wall of the lateral ventricle were completely exposed along with the choroid plexus (fig. 2). The foramen of Monro was small and patent. The cavity was then filled with saline solution, and the dura was partially reapproximated. Four sets of holes were drilled in the bone, through which braided silk suspended the flap of bone. The patient was given 1,100 cc. of whole blood during the operation and 500 cc. of a 10 per cent solution of dextrose intravenously.

Pathologic Examination.—The specimen consisted of the left cerebral hemisphere, weighing 700 Gm. A large firm mass with indistinct boundaries was palpable in the midportion of the superomedial aspect of the hemisphere. The tumor was approximately 7 cm. in height, 7.5 cm. in anteroposterior extent and 3.5 cm. in thickness. It extended from the precentral sulcus to 1.5 cm. behind the postcentral sulcus. Laterally, the areas of the cerebral cortex involved included the upper portions of the anterior central gyrus and of the postcentral gyrus, the anterior portion of the superior parietal lobule and the anterosuperior tip of the inferior parietal lobule. On the medial aspect of the specimen the tumor was seen through the posterior two thirds of the paracentral lobule, a large portion of the precuneus and the posterior part of the cingulate gyrus, extending well down to the corpus callosum.

Coronal sections showed the tumor to be toward the medial aspect of the specimen, with extension downward to involve the corpus callosum and a major portion of the thalamus in this area and to involve partially the radiations of the midportion of the internal capsule. The lateral ventricle was not actually invaded, but the swelling of the adjacent tissues had caused a displacement of the body of the ventricle downward and to the right. The microscopic diagnosis was medulloblastoma of the cerebrum.

Postoperative Course.—Several hours after the operation the blood pressure had returned to normal, and the patient answered "all right" to all questions. She showed her teeth when asked (fig. 3*A*) and drank water but would not protrude her tongue.

The day following the operation she appeared more alert to the examiners and to a relative than before operation (fig. 3*B*). "Yes" and "no" were added to her vocabulary.

Neurologic Examination on the Second Day After Operation (Nov. 19, 1933).—Cranial Nerves:

First Nerve. The nerve could not be tested.

Second Nerve. The limitations of the fields of vision could not be determined. There was choking of 2 diopters of the left optic disk but no measurable elevation of the right disk.

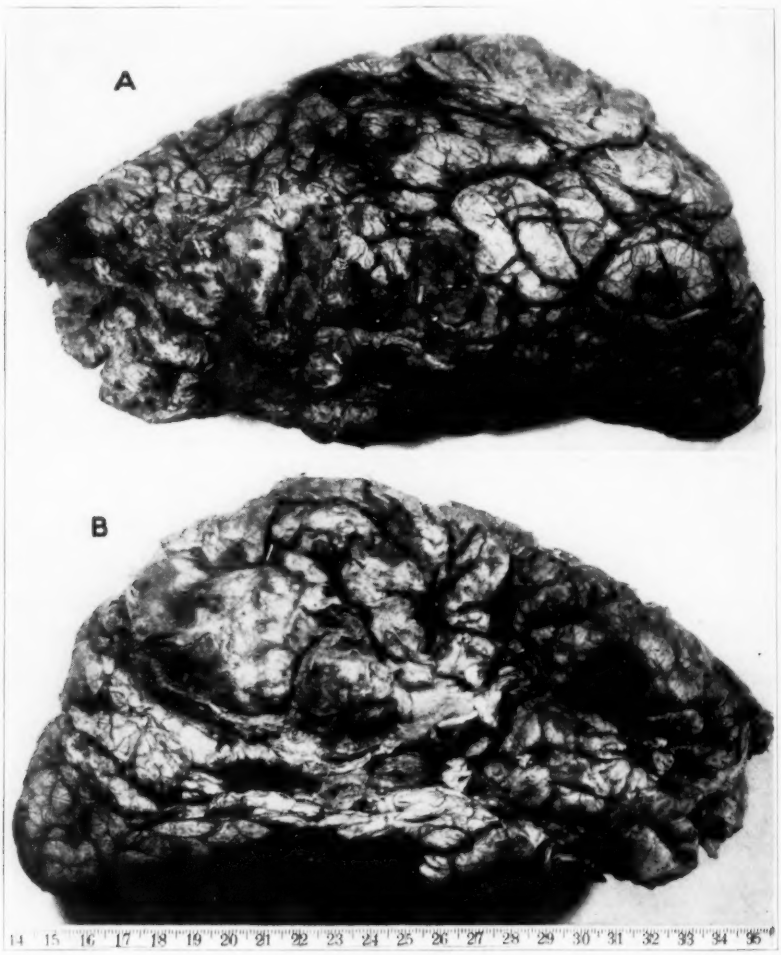

Fig. 1.—*A*, showing a lateral view of the left cerebral hemisphere after fixation in formaldehyde. *B*, medial view of the left hemisphere showing extensive involvement with the tumor.

Third, Fourth and Sixth Nerves. Extra-ocular movements were normal. The pupils were equal, regular and contracted and did not react to light.

Fifth Nerve. The corneal reflex was present on the right but absent on the left. There was no deviation of the lower jaw.

Seventh Nerve. There was slight weakness of the right side of the face, as before operation (fig. 3 *C*).

Eighth Nerve. It was my impression that the patient could hear with the left ear and apparently was free from dizziness.

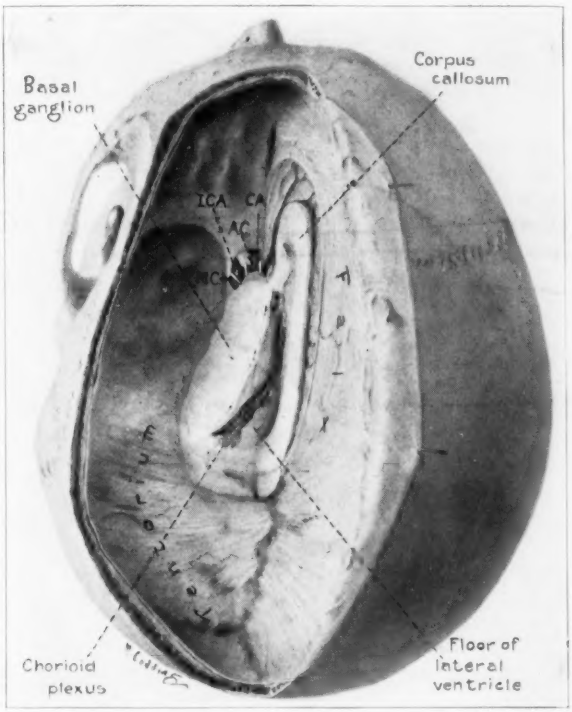

Fig. 2.—Drawing of the field of operation after removal of the left cerebral hemisphere.

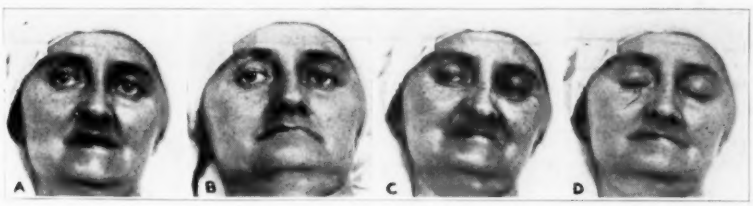

Fig. 3.—Photographs taken after the operation. *A*, the patient showing her teeth on the eighth postoperative day; *B*, the general facial expression; *C*, the facial expression in response to pain when the right arm was moved (the weakness of the right side of the face was not marked); *D*, the facial expression of the patient with the eyes closed on the eighth day after hemispherectomy.

Ninth Nerve. The pharyngeal reflexes were active. Determinations of taste were not made.

Tenth Nerve. The pulse and respirations were normal, but there were occasional regurgitation of fluid and apparent difficulty in swallowing.

Eleventh Nerve. No disturbance.

Twelfth Nerve. As before operation, the patient did not protrude her tongue.

Motor and Sensory Changes: The spastic paralysis on the right was replaced by a flaccid type. Passive movements of the right arm and leg were painful but less so than before operation (fig. 3 *C*). The reflexes of the upper extremities were more sluggish than before operation, especially on the right. The knee jerks were equal and moderately active. The right ankle was held in marked flexion. The Babinski response was present on the right and not on the left side. Stimulation of the right leg by squeezing, however, elicited dorsiflexion of the left great toe. This had been noted before operation.

Sensory examination to touch could not be carried out, but painful stimuli produced by pricking with a small pin were appreciated equally well over the entire body.

The essential changes in the patient's condition after operation were slight: reduction of an already limited vocabulary and less willingness or less ability to perform coordinated movements. There were decrease in the rigidity of the right side with less pain on passive motion and a general decrease in the excitability of reflexes. The patient's mental condition was not greatly altered, but she was definitely more comfortable. The drawn, painful expression of the face noted prior to operation had disappeared (fig. 3 *D*).

"Thank you" and "sleep" were added to the vocabulary on the second postoperative day. The patient repeated "sleep" several times during the neurologic examination, which obviously fatigued her.

On Nov. 20, 1933, the patient added the words "good-bye" and "please" to her vocabulary and showed a more accurate use of words. The left pupil reacted to light, but the right remained contracted.

On November 21 movement of the joints on the right side appeared more painful than on the left, but the painful reaction to pressure was about the same on the two sides. It was evident that the patient experienced emotional reactions. For example, while taking sips of water and replying "yes" and "no," apparently with a full understanding of their meaning, she abruptly closed her mouth and refused to drink or to speak following an outburst of laughter on the part of some observers in the room. It was more difficult to induce her to reply to simple questions when the room was full of people.

Readings of skin temperature were recorded to ascertain the vasomotor response of the extremities following hemispherectomy.[2] On the seventh day after left hemispherectomy the patient was placed in a room free from draughts at a temperature of 74 F. and a humidity of 58 per cent. Determinations of the temperature of the skin were made on both lower extremities, using the Tycos dermatherm. The temperatures of both great toes, after exposure of the extremities to the air of the room, were 32.5 C. (90.5 F.). Other corresponding points on the two sides likewise showed the same temperature. There were no evidences of abnormal redness, increased heat or sweating on the contralateral side. The forearms of the patient were then placed in hot water at 43 C. (109.4 F.) and temperatures of the skin taken on the lower extremities at one minute intervals over a period of one-half hour (technic of Gibbon and Landis[3]). There was the usual initial

2. Zollinger, Robert, and Schnitker, Max T.: Skin Temperature Reactions Following Removal of the Left Cerebral Hemisphere, Science **79**:540 (June 15) 1934.

3. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in Lower Extremities in Response to Immersing Forearms in Warm Water, J. Clin. Investigation **11**: 1019 (Sept.) 1932.

drop in temperature, averaging 1 C. (1.8 F.), following the sudden stimuli of placing the forearms in the hot water.[4] The temperature then began to rise in the normal way and reached 35.6 C. (96.8 F.) on the right and 35.4 C. (95.7 F.) on the left side (a rise of 3 C., or 5.4 F.). Redness and texture of the skin were equal on the two sides, but no sweating was demonstrable. The body temperature rose from 101.6 to 102.2 F. (rectal).

Seven days later the patient was placed in the same room at 76 F. and 56 per cent humidity. Initial temperatures of the skin of the great toe were 31.5 C. (88.7 F.) on the right and 31.3 C. (88.3 F.) on the left side. The forearms were then immersed in cold water at 16 C. (60.8 F.) and temperatures taken at one minute intervals for thirty minutes. Immediately following immersion of the fore-

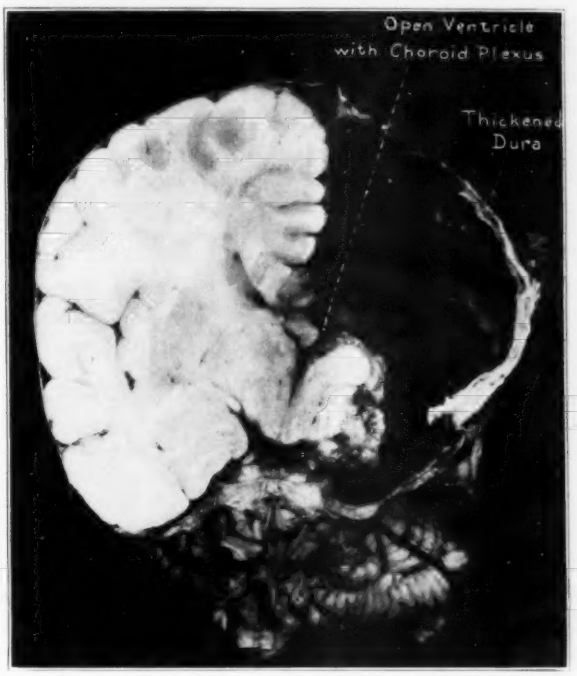

Fig. 4.—A cross-section of the brain at autopsy.

arms in cold water there was generalized vasoconstriction with a fall in temperature of 0.9 C. (1.6 F.) on both sides. The temperature began rising slowly and reached its maximum of 32.1 C. (89.8 F.) on the right and 31.7 C. (89.06 F.) on the left side in seventeen minutes. This gave an average rise of 1.5 C. (2.7 F.) above the coldest temperature after immersion in cold water. There was a similar rise in body temperature from 101.2 to 101.6 F. (rectal). These determinations showed that after hemispherectomy in a human being there appeared to be no measurable alterations in the regulation of peripheral temperature on either the ipsilateral or the contralateral side.

4. Pickering, G. W., and Hess, W.: Vasodilatation in the Hands and Feet in Response to Warming the Body, Clin. Sc. **1**:213 (Dec.) 1933.

Laboratory Findings.—The urine was always loaded with albumin and white blood cells. The Wassermann reaction of the blood was negative. The blood sugar eleven days after operation was 121 mg. per hundred cubic centimeters.

Thick yellow fluid was aspirated from the cranial cavity on the sixth, eleventh, thirteenth and fifteenth days after operation by introducing a needle directly through the left temporal muscle in the region of the decompression. During this time the pulse rate, which at first had remained around 110, gradually increased to between 130 and 140. The respiratory rate during the first five days averaged between 24 and 28 per minute, but it gradually rose to 40 per minute. The rectal temperature remained around 101 F. for four days, then ascended to 103 F. and 104 F. on the fifth and sixth days, falling to normal on the seventh day following the first cranial aspiration.

Course.—Severe diarrhea developed and persisted after the tenth day. The course was gradually downhill, and the patient died on Dec. 4, 1933, the seventeenth day after operation. Postmortem examination was limited to the head and neck.

Necropsy.—The left cerebral cavity was filled with grayish turbid fluid in which there were a large number of gram-positive cocci and gram-positive bacilli. The longitudinally exposed falx was compressed slightly toward the right. There was extensive thrombosis in the large venous channels. Slight discoloration of the meninges indicated a diffuse purulent meningitis. The only remaining cerebral tissue on the left side was the most medial parts of the thalamic nuclei and a small part of the globus pallidus (fig. 4). The midbrain and the pituitary body and its stalk appeared to be normal. The pituitary body and its stalk were intact when examined after fixation in situ. The anterior communicating artery was doubly clipped, but the right anterior cerebral artery was not obstructed. Sections of the right cerebral hemisphere showed no areas of softening.

COMMENT

The most interesting observation during the postoperative period was the ability of the patient to speak. She was definitely right-handed and had suffered a severe reduction of vocabulary as a result of infiltration of the left hemisphere by a tumor. Therefore one might have expected complete aphasia following the removal of the entire left hemisphere exclusive of the basal ganglia. The first difficulties in speech were noted by the family on July 23, 1933, eighty-five days prior to removal of the left hemisphere. At that time the patient had aphasia, as evidenced by her asking for one article and meaning another. Following the subtemporal decompression on the left side (July 24, 1933) and roentgen therapy she slowly improved, but there was a complete aphasia when she was discharged from the hospital on Sept. 30, 1933. She improved for a period of two weeks, becoming more alert and conversing with relatives; although she had considerable difficulty in remembering the names of articles, she was able to talk intelligently. A gradual decline followed, in which she cried frequently and expressed great apprehension about her future. The vocabulary gradually became lim-

ited to monosyllables like "drink, bed, sleep, yes" and "no." When examined on Nov. 15, 1933, prior to operation, she could not spell her name.

Several hours after operation she answered "all right" to all questions. "Yes" and "no" were added the following day, but they were not always used properly. She was taught by nurses to say "thank you" and "please." It was my impression that the vocabulary could have been gradually increased with training. Perhaps there had been a gradual development of a speech center in the right hemisphere during the months prior to removal of the left hemisphere. The mental capacity of the patient was greatly altered before operation, and the aphasia made it difficult to evaluate the status of her mentality after removal of the left hemisphere. She seemed definitely more calm after operation, but she was less willing, or less able, to perform coordinated movements. The patient did experience emotional reactions, but they were not marked.

The functions of the cranial nerves which we were able to test were markedly preserved. The extra-ocular movements and the general facial expression, except for a very slight weakness of the right side of the face, were normal. The corneal reflex on the left side was absent.

The spastic paralysis on the right side was replaced by a flaccid type of paralysis similar to some of the cases reported following the removal of the right cerebral hemisphere. The presence of acute pain with motion of the joints or compression of the deep muscles demonstrated the existence of a center of sensation below the cortex.

The readings of skin temperature taken after the removal of the left cerebral hemisphere failed to show a measurable alteration in the peripheral temperature reaction on either the ipsilateral or the contralateral side.[2] The changes in temperature noted over the dorsum of the right foot at the time of the first admission to the hospital in June 1933 might represent early vasomotor changes of cortical origin due to involvement of the left premotor area by the tumor. A compensatory mechanism regulating temperature may have been formed during the five months prior to removal of the hemisphere.

SUMMARY

The left cerebral hemisphere was removed in a right-handed woman. Her vocabulary, skin temperature reactions and neurologic examination are recorded during the seventeen days which she survived. The findings were as follows:

An elementary vocabulary was retained, which was partially increased by training in speech.

It was difficult to evaluate the mental capacity of the patient. She was more calm after operation but was less willing to perform coordinated movements. She did experience emotional reactions, but they were not marked.

The functions of the cranial nerves were well preserved except for slight weakness of the right side of the face and the absence of the corneal reflex on the left.

The spastic paralysis on the right side was replaced by flaccid paralysis.

The presence of acute pain with motion of the joints or compression of the deep muscles demonstrated the existence of a center of sensation below the cortex.

Studies of the vasomotor responses of the extremities by determinations of skin temperature did not show measurable alterations in peripheral temperature regulation on either the ipsilateral or the contralateral side.

Clinical Note

SIMPLE METHOD OF STAINING MACROSCOPIC BRAIN SECTIONS

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By a simple procedure to be described it is possible to obtain preparations of the brain in which the contrast between the white and the gray matter is sharp, with the coloring brilliant and the effect lasting. Specimens so prepared are suitable for use in classes and for display in museums (fig. 1). The technic may be extended to lesions of the brain (figs. 2 and 3).

While preparing sections of the brain for the museum, I endeavored to repeat the experiments with cobalt, lead and antimony stains described and vividly

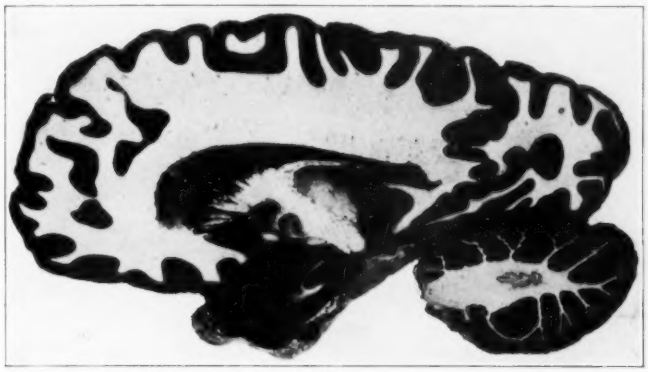

Fig. 1.—Parasagittal section of the right cerebral and cerebellar hemispheres. The cortical tissue is a brilliant blue and the central nuclei, such as the caudate nucleus and thalamus and the dentate nucleus of the cerebellum, are clearly and permanently stained.

depicted in an article by Blair.[1] As Blair pointed out, these stains, though not producing a permanent effect, give a good color contrast while the reaction lasts. Sections prepared by me according to this method faded in the course of a few days. Similarly the prussian blue stain, as applied by Sincke[2] and Mainland,[3] employing ferric chloride followed by potassium ferrocyanide, gives a vivid picture but fades rapidly. With Mulligan's method,[4] as used by Green,[5] which consists in

From the Department of Anatomy and Division of Neuropathology, University of Toronto.

1. Blair, D. M.; Davies, F., and McClelland, E. W.: J. Anat. **66**:478 (July) 1932.
2. Sincke: Anat. Anz. **61**:311, 1926.
3. Mainland, D.: Anat. Anz. **65**:841, 1928.
4. Mulligan, J. H.: J. Anat. **65**:468 (July) 1931.
5. Green, H. L. H. H.: J. Anat. **67**:346 (Jan.) 1933.

treating the section with phenol prior to using tannic acid followed by iron alum, I met with great success. This method was entirely satisfactory in that the color was permanent and gave a marked differentiation between white and gray matter, but the general appearance of the specimen was rather dull.

Phenol seems to confine the stain more sharply to the gray matter. According to Mulligan, this is because the phenol and lipoids unite in some manner to

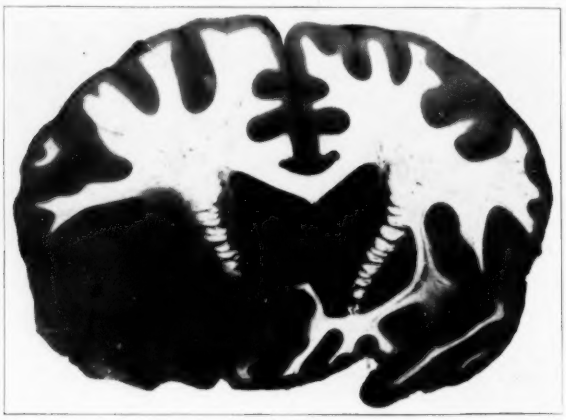

Fig. 2.—An astrocytoma of the left frontal lobe. Such tumors show a poor color and differentiation from the surrounding white matter, and therefore they make unconvincing preparations for museums. The tumor tissue is satisfactorily stained by this method.

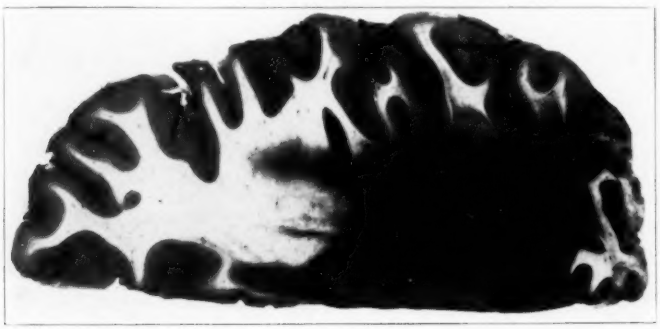

Fig. 3.—A cerebral hemisphere from a patient with Schilder's disease. The demyelinated area of white matter in the occipital and the parietal lobes is densely stained with prussian blue.

form a protective film over the white matter. I decided to treat sections first with a solution of hot phenol and then to employ the Sincke prussian blue stain. This gave striking results. The selective action of the ferric chloride was equal to that of tannic acid, and the brilliance of the prussian blue was increased. For a year the preparations have been stored in 70 per cent alcohol and exposed daily to the sunlight without showing signs of fading. On the con-

trary, the cortex has taken on a slightly deeper tone and the white matter a more creamy appearance. The following method is the one that has finally been decided on for routine work.

METHOD

Cut a brain, which has been thoroughly fixed in a dilute solution of formaldehyde U. S. P. (1:10), into slices of the thickness desired with a knife of the type used for work on the brain, which has been smeared with glycerin. The cutting should be done with one draw to avoid leaving marks of the knife.

Wash the specimen for from twelve to twenty-four hours in running water and place in distilled water for one hour, changing the water three times during the hour.

Then submerge the sections for two minutes, at from 60 to 65 C., in Mulligan's solution of phenol, covering with at least 2½ inches of solution. The formula for Mulligan's solution[3] is as follows: 4 per cent phenol crystals; 0.5 per cent copper sulphate crystals, and 0.125 per cent concentrated hydrochloric acid dissolved in distilled water.

Place the sections in a large volume of cold tap water for one minute and then in a 1 per cent solution of ferric chloride in distilled water for two minutes, and wash them in running water for five minutes. Place them in a 1 per cent solution of potassium ferrocyanide in distilled water until the gray matter is a brilliant blue (this should not take longer than three minutes) and wash them in running water for twenty-four hours. Finally, preserve them in 70 per cent alcohol.

PREVENTION OF POSTOPERATIVE EXTRADURAL HEMATOMA

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The incidence of extradural clots following exploratory craniotomy in cases of focal epilepsy in which no increased intracranial pressure exists and no organic lesion is found is high, even if before closure of the osteoplastic bone flap the utmost caution is exercised in controlling all the small bleeding points. The

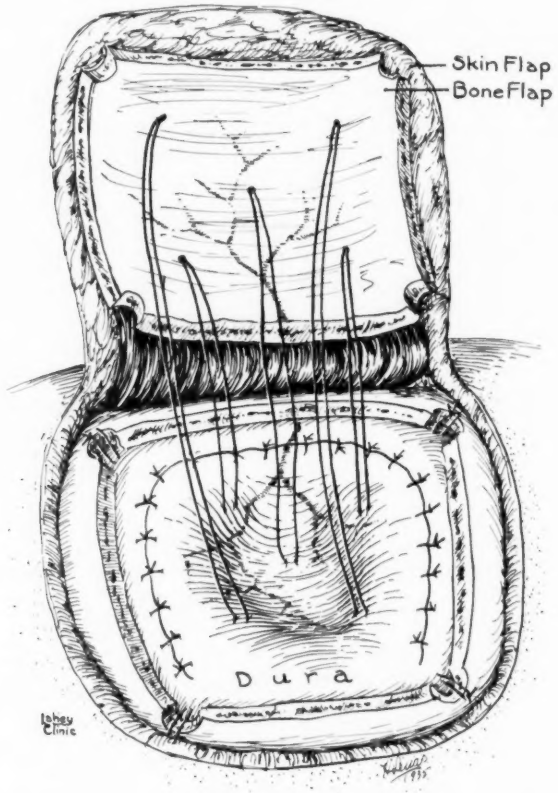

Fig. 1.—Drawing of the openings in the bone, with black silk sutures placed through the dura at points corresponding to the openings in the bone. These sutures are brought out to the surface of the scalp through the small drill openings in the bone. The figure also shows the sutures in the large bur openings, which have been placed through the dura and tied to the galea, preventing venous oozing beneath the edges of the bone. This plan has been practiced for a considerable time in neurosurgical clincs.

suturing of the dura to the galea or periosteum has been consistently practiced in neurosurgical clinics, and it has been invaluable in controlling bleeding from under edges of the bone. Bleeding may occur several hours after the closure and an extradural clot may develop even though the oozing from the inner surface

of the bone flap has been thoroughly stopped with bone wax and electrocoagulation and a considerable portion of the bone has been stripped from its muscular attachments.

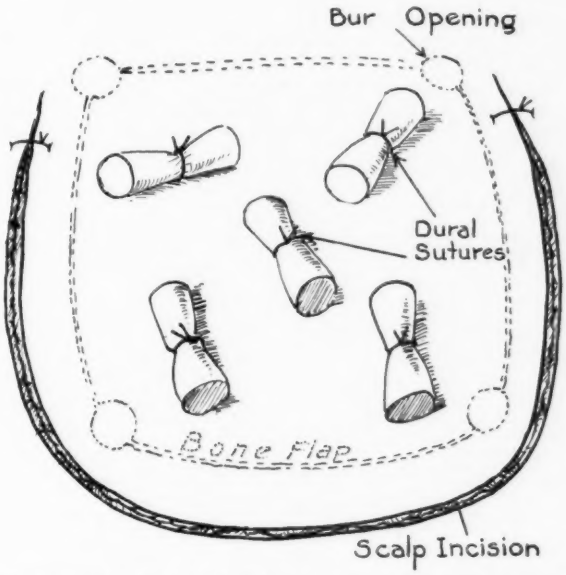

Fig. 2.—The osteoplastic bone flap has been replaced. The dural sutures have been brought out through the small drill openings and tied over cotton pledgets saturated in alcohol.

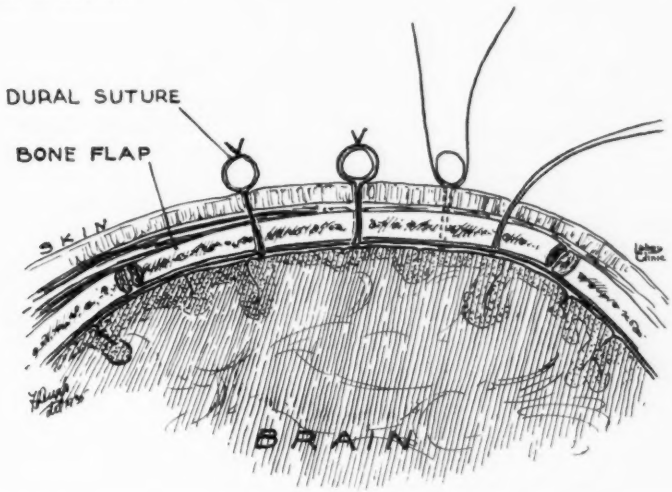

Fig. 3.—A cross-section showing sutures holding the dura firmly against the inner surface of the bone.

By making several small openings with a drill through the osteoplastic bone flap, the dura can be sutured firmly against the inner surface of the bone, making it practically impossible for clots sufficiently large to cause symptoms to form. The drawings are self-explanatory and show the technic employed.

Abstracts from Current Literature

TUMORS OF THE FRONTAL LOBE: CLINICAL OBSERVATIONS IN A SERIES VERIFIED MICROSCOPICALLY. H. C. VORIS, A. W. ADSON and F. P. MOERSCH, J. A. M. A. **104**:93 (Jan. 12) 1935.

Voris, Adson and Moersch submit an analysis of the clinical observations in a series of 314 cases of tumor of the frontal lobe, give the relative frequency of the occurrence of these growths and emphasize the predominant symptoms. They pay special attention to certain signs and symptoms that universally have been considered to be diagnostic of lesions of the frontal lobe and to the relation of age and sex of the patient to the pathologic type of tumor. The duration of life compatible with intracranial tumor depends on the life cycle or rapidity of the growth of the neoplasm, the situation of the tumor and the treatment that is given: surgical procedure and the dose of radiation. The initial complaint may often be the only symptom for a considerable period of time. In 112 of 312 cases the initial complaint was some type of convulsive seizure. Grand mal seizure was by far the most prevalent type, and it occurred as the initial complaint in 75 cases, or about 25 per cent of all cases in the series. It was the initial complaint in approximately a fifth of the cases in which the tumor was confined to the prefrontal-frontal area (silent cortex). Jacksonian fits occurred in 29 cases and petit mal in 8 as the initial complaint. Headache was the next most common initial complaint, occurring in 85 cases, or 27 per cent of the cases in the series. Mental change of some type was the next most common initial complaint, occurring in 31 cases. Failing vision was the initial complaint in 25 cases, hemiparesis occurred in 13 cases, and extracranial swelling occurred in 10. The initial complaint in the remaining cases was as follows: general debility in 5 cases, dizziness in 5, syncope in 4, loss of sense of smell in 4, paresthesia in 4, drowsiness in 3, aphasia in 3, ataxia in 3, vomiting in 2, and stiff neck, insomnia and uncinate fits in 1 each. When the various complaints are considered, headache was the most common complaint in all groups except those in which the tumor was confined to the premotor or motor areas or to a combination of prefrontal and premotor areas. Convulsive attacks ranked next in frequency, occurring in 69 per cent of all cases and in 55 per cent of cases in which the tumor was confined to the prefrontal-frontal area. Mental change was the next most frequent complaint. Nausea and vomiting were present in 50 per cent of all cases and in 58 per cent of those in which the tumor was known to be confined to the prefrontal-frontal area. Visual disturbance of some sort was present in 43 per cent of all cases and in 67 per cent of those in which the tumor was known to involve only the prefrontal-frontal area. Weakness or paralysis of the contralateral side of the face was complained of by 35 per cent of the patients, but a similar complaint was made by only 9 per cent in whom the growth was known to involve the prefrontal-frontal area alone. The most frequent change found at examination, exclusive of mental changes, was some degree of choking of the optic disks. Reflex disturbances on the contralateral side, either increase in tendon reflexes or decrease in cutaneous reflexes or the presence of such pathologic reflexes as Hoffmann's, Babinski's or Rossolimo's, were the next most important changes from the standpoint of frequency. Defects of the visual fields were present in 32 per cent of cases in the entire series and in almost half of those in which the growth was confined to the prefrontal-frontal area. Of the cerebellar signs (ataxia and incoordination and adiadokokinesis of the homolateral extremities) one or more were present in 32 per cent of all cases and in about the same percentage of those in which the tumor was confined to the prefrontal-frontal area. Disturbance in speech of some degree was present in 29 per cent of cases in the entire series and in 15 per cent of those in which the neoplasm was confined to the prefrontal-frontal area. External ocular palsies,

usually of the external rectus muscle but occasionally of muscle innervated by the oculomotor or trochlear nerve, were present in about a fifth of the cases in the entire series and in a little more than a fourth of those in which the tumor was confined to the prefrontal-frontal area. Sphincteric disturbances, often considered a part of the classic picture of tumor of the frontal lobe, were present in 20 per cent of all cases, and sensory disturbances on the contralateral side of the body in 15 per cent. Only 1 case, in which the growth was confined to the prefrontal-frontal areas, presented sensory disturbances. Special signs, such conditions as reflex or so-called forced grasping, apraxia, deviation of the head or eye, and perseveration or retardation of motor movements, appeared singly or in combination in 15 per cent of the cases in the entire series, in 6 per cent of those in which the tumor was confined to the prefrontal-frontal area, and in 19 per cent of those in which the premotor or motor areas were to some extent involved. Nystagmus occurred in 13 per cent of all cases and in practically the same percentage of those in which the growth involved only the prefrontal and frontal areas. In addition to the 198 patients with a complaint of mental change, the results of examination indicated that 21 more presented objective evidence of mental abnormality. Taking the series as a whole, lesions associated with mental changes were on the left side in 40 per cent of the cases, on the right side in 34 per cent and bilateral in 26 per cent. Indifference to environment was the most frequent mental symptom. Of the entire series there was roentgen evidence pointing to the presence of an intracranial tumor in 124 cases. The ratio of direct to indirect evidence was a little less than 1 : 2. Of the 109 patients with endothelioma, 63 gave roentgenographic evidence of an intracranial lesion, with practically equal division between the direct and the indirect classes of evidence. Of the 28 patients with oligodendroglioma or oligodendroblastoma, 14 gave roentgenographic evidence of the lesion, 10 indirect and 4 direct.

EDITOR'S ABSTRACT.

DEGENERATIVE DISEASES WITH SPECIAL PREDILECTION FOR MOTOR CONDUCTION TRACTS AND NUCLEI AND COMBINED SYSTEM DISEASES. GEORGE B. HASSIN, Monatschr. f. Psychiat. u. Neurol. **86**:255 (Sept.) 1933.

Amyotrophic lateral sclerosis is a degenerative disease which attacks the motor cells of the cerebral cortex, medulla oblongata and spinal cord. The degeneration of the pyramidal tracts is secondary. Reactive changes in the glia are observed. Perivascular infiltrations are usually lacking, though they may be present as an indication of symptomatic inflammation. There is degeneration of the anterior roots, the motor nerves and the muscles supplied by these nerves. Other alterations, such as degeneration of the posterior columns or cerebellar tracts, occur occasionally, but they are considered to be due to accidental or accessory factors. Endotoxins or metabolic disturbances may be concerned in the causation of amyotrophic lateral sclerosis. Syphilis plays no part in its etiology. The disorder described as syphilitic amyotrophic lateral sclerosis differs clinically and pathologically from the classic forms of the disease. Progressive bulbar paralysis is characterized by severe degeneration of the bulbar motor nerves and their nuclei, with less marked changes in the motor cells of the cerebral cortex and the spinal cord. It is now generally agreed that this disease is merely a form of amyotrophic lateral sclerosis. In progressive muscular atrophy (Duchenne-Aran type) the chief changes occur in the anterior horns of the spinal cord, the anterior roots, the motor nerves and the corresponding muscles. There are less pronounced bulbar and cortical alterations. The disorder known as chronic anterior poliomyelitis does not differ essentially from progressive muscular atrophy. Therefore, the former term should be dropped from the nomenclature. The histologic changes observed in the infantile or heredofamilial form of muscular atrophy (Werdnig-Hoffmann type) are similar to those in the Duchenne-Aran type of progressive muscular atrophy. Hassin believes that the former is merely a type of spinal muscular atrophy occurring in infants and in children. He comes to the conclusion that amyotrophic lateral sclerosis, bulbar paralysis and progressive spinal muscular atrophy, including the Werdnig-

Hoffmann type, are manifestations of the same disease process. In all of these disorders there is degeneration of the motor cells of the cerebral cortex, medulla oblongata and spinal cord. If all three levels are involved simultaneously, the picture of amyotrophic lateral sclerosis is produced. The clinical picture of bulbar paralysis occurs when the lesions predominate in the bulbar motor nuclei, whereas that of progressive muscular atrophy is observed when the changes are confined chiefly to the nerve cells of the spinal cord. The question arises whether there are conditions in which the alterations at first predominate in the cortical motor cells and lead only later to the complete picture of amyotrophic lateral sclerosis. Hassin thinks that such conditions are actually encountered, having been described as spastic paraplegia (lateral sclerosis or the Erb-Charcot disease) and as progressive ascending and descending hemiplegia of Mills. Both are to be regarded as atypical forms of amyotrophic lateral sclerosis.

The term combined system disease should be limited to disorders that affect several fiber systems. The best known forms are subacute combined degeneration of the spinal cord and hereditary ataxia (Friedreich's and Marie's form). Strümpell's spastic paraplegia, also known as the familial form of spastic paraplegia, is an unusual type of combined system disease. Pellagra, dementia paralytica, other syphilitic disorders of the spinal cord and trauma may be associated with combined system disease. Friedreich's ataxia is a typical example of this order. Here the posterior columns and the dorsal spinocerebellar tracts are degenerated. The crossed pyramidal tracts show less marked damage, and there may be involvement of the direct pyramidal tract and of Gower's tract. The nerve cells of Clarke's column and the anterior and posterior roots are damaged. Reactive glial and vascular changes occur, but inflammatory cell infiltrations are not observed. The medulla oblongata, pons, cerebellum and cerebrum are not as a rule affected. In Marie's hereditary ataxia there are degeneration and atrophy of the cerebellum and degeneration of the dorsal spinocerebellar tract, Gower's tract and the adjacent white matter. There may be atrophy of the cells of Clarke's column and a diminution in the number of the dorsomesial cells of the anterior horn. In Strümpell's spastic paraplegia there is involvement of the crossed and direct pyramidal tracts, Goll's tract and the dorsal spinocerebellar tract. However, disturbances of the pyramidal system always occupy the foreground, clinically as well as pathologically. Cases have been described in which the clinical picture of familial spastic paraplegia was succeeded by that of amyotrophic lateral sclerosis. In such cases pronounced changes in the nerve cells of the precentral gyrus were noted. These observations suggest that the primary process in familial spastic paraplegia may be operative in the cerebral cortex rather than in the different fiber systems of the spinal cord. It is probable that the involvement of Goll's tract is based on accessory factors, representing a condition analogous to that which leads to the accessory changes sometimes seen in cases of amyotrophic lateral sclerosis.

ROTHSCHILD, Foxborough, Mass.

DECOMPRESSION OF THE FACIAL NERVE. EDWARD CECIL SEWALL, Arch. Otolaryng. **18**:746 (Dec.) 1933.

The motor fibers of the seventh nerve to the facial musculature arise in the pons in a cell column common to all the motor cranial nerves except the hypoglossal nerve and the nerves to the eye. There is a separation of the higher centers controlling each nucleus, so that the temporal fibers to the occipitofrontalis, orbicularis oculi and corrugator supercilii muscles are not involved in cases of cortical hemiplegia. Reichert and Poth questioned the classic distribution of the taste fibers. Apparently they have proved that the glossopharyngeal nerve furnishes distribution to the submaxillary and sublingual glands. In a case reported by Reichert relief from neuralgia of the tympanic plexus followed division of the root of the ninth nerve. Hesse reported a case in which section of the neck of the glossopharyngeal nerve obviously distal to the branching of Jacobson's nerve resulted in a diminution of secretion from the parotid gland.

Reichert and Poth observed that secretion from the parotid, submaxillary and sublingual glands was diminished on the homolateral side after intracranial section of the glossopharyngeal nerve. They noted that secretion from all the salivary glands was reduced on section of the chorda tympani nerve distal to its departure from the fallopian canal. They observed a case of Bell's palsy in which taste was retained, though all homolateral salivary secretion was diminished. This case indicates that secretory fibers reach the chorda tympani nerve via the facial nerve distal to the chorda tympani. They failed to observe any salivation in a known case of neuralgia of the tympanic plexus.

Tic douloureux of glossopharyngeal origin was described first in 1910, by Weisenburg. The upper lid does not move downward on wilful stimulation to close the eye in the presence of complete facial paralysis. The upper lid follows movements of the hand downward past the midline, even in the presence of complete facial paralysis. Gravity plays no significant rôle in the downward movement of the lid. Downward movement of the lid induced by downward rotation of the eyeball, because of cohesion of the conjunctiva or because of some other direct influence, has apparently been disproved. It has been suggested that associated muscular movement and stressed contracture may account for movements of the lids so that the orbicularis oculi muscle might be stimulated through associated control in a case of recent facial paralysis.

Case 1.—A radical operation on the mastoid was performed on the right ear of a patient on Aug. 18, 1932; this was followed by a second operation on the right ear on November 14. Complete facial paralysis appeared twelve hours after the operation. There had been a slight twitching at the time of operation. On December 19, practically one month after the occurrence of the paralysis, the wound was reopened and the facial nerve was uncovered from the stylomastoid foramen to a point well forward of the knee. The middle third of the vertical portion of the nerve was found to be swollen and damaged. The nerve was freed from bony pressure well above and below the injured portion. It was found to be in continuity. The sheath was opened, and the nerve was covered by a Thiersch graft that extended forward to line the middle ear. The wound was immediately closed posteriorly except for a small tissue drain in the lower angle. The wound healed without incident, but troublesome granulation tissue in the middle ear still furnishes some secretion. The facial paralysis was complete and unchanged when the patient was last seen on May 29, 1933, more than five months after decompression. On Sept. 11, 1933, there was definite evidence of returning function of the paralyzed facial nerve.

Case 2.—A simple operation on the mastoid was performed on a patient on Feb. 24, 1933. A slight twitching occurred during the operation. Complete facial paralysis appeared nine hours after the operation. On March 8 decompression of the right facial nerve was performed. The electric bur was of assistance because of the unusual depth of the wound. There was considerable hemorrhage from the stylomastoid artery, which was controlled at the source. The nerve swelled on being released from the canal. It showed injury 2 mm. below the knee and for a distance of 4 mm. It was laid bare 4 mm. proximal to the wound and distal to the stylomastoid foramen. The nerve was in continuity. The sheath was slit, and the posterior part of the wound was closed except where a small rubber drain was inserted in the lower angle. There was no return of function when the patient was last seen on June 2, nearly three months after decompression.

Hunter, Philadelphia.

Studies on Thyrotropic Hormone of Anterior Pituitary. J. B. Collip and E. M. Anderson, J. A. M. A. **104**:965 (March 23) 1935.

Collip and Anderson followed the changes in the metabolic rates of a group of rats given injections of large doses of a purified extract of the thyrotropic hormone. In studying the nature of negative response to the thyrotropic hormone, they found that the serum of animals which have been given injections of this

extract for a long period of time contains a substance that is capable of inhibiting the action of the hormone. A horse was given injections of the extract for four months and after the first month antithyrotropic substance was found to be present in its serum. Extracts of the antithyrotropic serum of the horse have been prepared which, when given in doses of 0.4 cc., are capable of inhibiting the action of 100 units of thyrotropic hormone in the normal rat. Larger amounts of the extract, up to 4 cc. daily, not only inhibit the action of 100 units of thyrotropic hormone injected into normal rats but at the same time apparently inhibit the thyrotropic hormone of the animal's own pituitary gland, causing a fall in metabolic rate to minus 24 per cent. The authors have obtained the inhibitory substance in the serum of animals of different species into which thyrotropic hormone has been injected. In addition to the rat and horse, the guinea-pig, rabbit and dog have been studied. The mechanism of the action of the antithyrotropic substance is not understood. It does not inhibit the action of the thyroxine. Rats given injections of thyrotropic hormone for periods of from forty to seventy days showed practically the same response to a given amount of thyroxine as normal animals. The giving of antithyrotropic serum in conjunction with thyroxine did not prevent a rise in metabolism. A study of the combined action of the thyrotropic and antithyrotropic hormones on the thyroid may clear up some of the discrepancies between changes in function of the thyroid gland and the cellular activity. When the animal has built up its own antithyrotropic substance as a result of prolonged injections of thyrotropic hormone, the thyroid undergoes hyperinvolution until it resembles somewhat the atrophic thyroid seen in the hypophysectomized animal. In an attempt to find the amount of antithyrotropic hormone which would just inhibit the action of a definite amount of thyrotropic hormone, the authors observed that a given amount of antithyrotropic hormone may be sufficient to prevent the rise in metabolic rate without inhibiting the production of hyperplasia of the thyroid by the thyrotropic hormone. Hypophysectomized rats that received both thyrotropic and antithyrotropic hormones for from seven to ten days showed hyperplastic changes at the end of this period, associated with a lowered metabolic rate, which was depressed in some instances to 38 per cent below normal. In a large series of rats and guinea-pigs in which they studied the morphologic changes of the thyroid coincident with changes in the metabolic rate during treatment with thyrotropic hormone, they found it difficult in many cases to correlate the microscopic appearance with the physiologic changes, as indicated by the metabolic rate. A group of goitrous rats in which the morphology of the thyroid resembled the hyperplasia seen in exophthalmic goiter showed a subnormal metabolism; in some cases the rates were as low as minus 17 per cent. A severe hyperthyroidism developed in these animals when thyrotropic hormone was given; the metabolic rates varied from plus 120 to plus 200 per cent. The animals that died, death being due apparently to thyrotoxicosis, showed beginning involutional atrophy of the thyroid. Evidence has been gathered in the study of the physiologic properties of the thyrotropic hormone which suggests that the anterior pituitary may play an etiologic rôle in exophthalmic goiter. The finding of an antithyrotropic hormone brings in another factor that needs to be correlated with the present knowledge of thyroid disease. The authors employ in their laboratory methods for assaying the blood serum for the presence of certain inhibitory substances. It appears to them that progress in clinical endocrinology will be more rapid as well as more certain if attention is diverted for the time being from treatment to a study of the blood of the patient so far as reliable methods are available.

EDITOR'S ABSTRACT.

PATHWAYS OF REFLEX PAIN IN VIDIAN NEURALGIA. HARRIS H. VAIL, Arch. Otolaryng. **21**:277 (March) 1935.

In this article Vail defends his position that pain may be felt reflexly through the vidian nerve and sympathetic fibers. Sluder described neuralgia of the sphenopalatine ganglion as a sharp, deep pain starting in the root of the nose and

radiating about and behind the eye over the temple to the ear and the mastoid process to the back of the head and neck and, in severe cases, to the shoulder and arm; it continues steadily for from hours to days and is not associated with any sensory disturbances or caused by external stimulation of the face. It is completely relieved in a few minutes by the injection of a few drops of 10 per cent solution of cocaine into the sphenoid sinus of the affected side.

The vidian nerve is in close relationship to the floor of the sphenoid sinus. The canal of the nerve may be projected into the sinus as a rounded ridge. In cases of vidian neuralgia the sphenoid is usually of markedly pneumatized type, favoring the development of latent sphenoiditis.

Kuntz and Fenton and Larsell are cited to prove that sensory fibers are carried in the great superficial petrosal nerve and that the sphenopalatine ganglion contains sympathetic fibers which continue to the palatine and postnasal nerves, as shown by the work of Kuré and Sakurasawa, who found that the unmyelinated fibers in both the vidian and the maxillary nerve completely disappear after extirpation of the superior cervical ganglion and hence are sympathetic or thoracolumbar autonomic fibers.

Various authors are cited who have shown that the sympathetic fibers may transmit pain and that there is a relationship between the orbital branches of the sphenopalatine ganglion and the terminal branches of the ophthalmic division of the trigeminal nerve and between the tympanic branch of the glossopharyngeal nerve and the geniculotympanic branch of the geniculate ganglion. Removal of the sphenopalatine ganglion does not result in any greater anesthesia than that which is produced by simple injection of an anesthetic into the ganglion. The pain in vidian neuralgia is deep and not located on the surface of the skin or the mucous membrane. Vail takes issue with Garber's statement that the maxillary nerve is in just as close proximity to the sphenoid sinus as the vidian nerve. The fact that in tic douloureux, an undoubted disease of the maxillary nerve, there is no overflow of pain down the neck and shoulder would point to the conclusion that it is not the nerve involved in Sluder's syndrome, or vidian neuralgia. Because of the anatomic relationship of the fibers of the superior and middle cervical sympathetic ganglia and the sympathetic fibers running in the great superficial petrosal nerve, Vail is convinced that irritation of the vidian nerve may result in reflex pain in the neck, shoulder and arm and in the distribution of the ophthalmic and the glossopharyngeal nerves.

Although the cutaneous sensory branch of the facial nerve may explain reflex otalgia, the evidence points more strongly to the participation of the glossopharyngeal nerve in the reflex pain in the ear in vidian neuralgia. In Reichert's case complete relief from severe neuralgia in the ear followed the intracranial sectioning of the glossopharyngeal nerve.

HUNTER, Philadelphia.

FUNDAMENTAL REMARKS ON THE PATHOGENESIS OF AMAUROTIC IDIOCY. K. SCHAFFER, Monatschr. f. Psychiat. u. Neurol. **84**:117 (Nov.) 1932.

The chief pathologic features of amaurotic family idiocy are the characteristic swelling of the ganglion cells and the filling of these cells with granules showing an affinity for hematoxylin. While similar changes occur in Niemann-Pick's disease, here other alterations are also observed. There are foam cells and fine dustlike granular deposits of lipoid in the meninges and the walls of the vessels. These features, which are characteristic of Niemann-Pick's disease, point to a mesodermal factor that is lacking in cases of amaurotic idiocy. The signs of metabolic disorder noted in the liver, spleen and lymph glands of patients with Niemann-Pick's disease fail to occur in pure cases of Tay-Sachs' disease. The fact that ganglion cell changes are observed in cases of Gaucher's disease and of Niemann-Pick's disease does not necessarily indicate a relationship to amaurotic family idiocy. Such changes are to be regarded as a general, and not a specific, type of reaction. Here Schaffer draws an analogy from another field, pointing out that fibrillary alterations of the Alzheimer type were at first considered pathognomonic of presenile disorders, though it is now known that they may occur in conditions inde-

pendent of presenility or senility. The case described by Smetana as one of splenohepatomegaly with amaurotic idiocy is excluded from the Tay-Sachs' group by Schaffer owing to the absence of macular alterations. According to Schaffer, no typical case of the infantile form of amaurotic idiocy has failed to show idiocy, macular changes and spasms. The histologic features of Niemann-Pick's disease point to a causal factor in mesodermal tissues outside the nervous system, the ectodermal alterations being secondary. In contrast to this, Tay-Sachs' disease is primarily and exclusively an ectodermal disorder, with the ganglion cells of the whole nervous system affected. The first visible alteration is swelling of the cytoplasm. Schaffer looks on this as a colloidal swelling of the hyaloplasm produced by the taking up of water. The granules are deposited or precipitated later. In the chronic juvenile form of amaurotic idiocy the tempo of the process is modified, the swelling is less marked and the deposits consist of more mature lipochrome pigment. Epstein and others have shown that a general phosphatide lipoidosis of the liver, spleen and bone marrow does not occur in Tay-Sachs' disease. The fact that Epstein was unable to find any increase in the phosphatide or cholesterol content of the brain in a case of amaurotic family idiocy indicates that the deposits are formed from substances originally present in the nervous system. The pronounced increase of lipoid in Niemann-Pick's disease owes its origin to the fact that the lipoid is brought to the brain by the histiocytic apparatus. In Schaffer's opinion, when Niemann-Pick's disease shows macular changes typical of amaurotic idiocy it represents a combination of two independent disorders, one (Niemann-Pick's disease) affecting the mesodermal and the other (Tay-Sachs' disease) the ectodermal germinal layers.

ROTHSCHILD, Foxborough, Mass.

THE RÔLE OF THE HYPOPHYSIS IN HYPERTHYROIDISM AND THE PARAHYPERTHYROID SYNDROME: A CONTRIBUTION TO THE STUDY OF HYPERTHYROIDISM. P. L. DROUET, Rev. franç. d'endocrinol. **12**:101 (April) 1934.

Drouet believes that the hypophysis plays a definite part in hyperthyroidism. In support of this conception he invokes the earlier studies of Comte, Stieda, Hofmeister and Parisot dealing with rapid hyperplasia of the hypophysis following anatomic or functional suppression of the thyroid gland. He mentions the recent work of Loeb and others, who proved the existence of a principle in the anterior part of the pituitary gland which stimulates the activity of the thyroid and was named by Max Aron *thyréo-stimuline*. He also refers to the work of Aron and Klein, who have demonstrated the presence of *thyréo-stimuline* in the blood, spinal fluid and urine. Discussing the clinical aspect, he emphasizes the great incidence of hyperthyroidism in women, apparently as a response to the greater demands made on the pituitary gland during menstruation, pregnancy and the menopause. The arterial hypertension is caused not by the hyperthyroidism per se but by the influence of the posterior lobe of the pituitary gland. Under therapy, for instance, while the symptoms of hyperthyroidism disappear, the hypertension may remain unchanged. Glycosuria in cases of hyperthyroidism is explained on the same basis. The cardinal symptoms of hyperthyroidism—the exophthalmos, tachycardia and tremor—are of neurovegetative origin and are seen in the so-called parahyperthyroid syndrome, which is not hyperthyroid in character according to Drouet.

Drouet's own contribution to the proof of the implication of the rôle of the pituitary gland in hyperthyroidism is the restriction of the visual field observed by him. In five of nine cases of hyperthyroidism, careful examination revealed a bitemporal heteronymous defect for white and to a lesser extent for red and green. Drouet claims that this defect is due to the swelling, probably hyperplasia, of the pituitary gland.

Another contribution in favor of the participation of the pituitary gland in hyperthyroidism is the so-called "melanophorotropic" reaction. This reaction consists of turning the frog's skin black following the administration of an extract from the pars intermedia or pars anterior into the dorsal lymph sac. The change

of color is due to enlargement of the pigment cells containing melanin. Drouet was able to demonstrate this reaction by injecting 3 cc. of nocturnal urine taken from patients with hyperthyroidism, while the same reaction remained negative when urine from normal controls was used.

Finally, he attempts to prove his conception by therapeutic results, claiming that treatment of the hypophysis with roentgen rays of high voltage has a remarkable effect in decreasing the basal metabolic rate in cases of hyperthyroidism.

NOTKIN, Poughkeepsie, N. Y.

CLINICAL OBSERVATIONS ON CHOREA OF PREGNANCY. R. THIELE, Monatschr. f. Psychiat. u. Neurol. **85**:170 (March) 1933.

Thiele discusses clinical observations made in twenty-one cases of chorea of pregnancy. Five of the patients had had chorea in childhood. The first attack of chorea gravidarum occurred in patients aged from 19 to 29 years. In thirteen instances the age of onset was between 19 and 23. The illness began during the first pregnancy in nine cases and during the second in seven cases. Eight patients showed the first symptoms in the fourth month of pregnancy. A later onset was not uncommon. Seven patients presented clinical evidence of cardiac disease. The symptoms may begin gradually or suddenly. They did not differ essentially from those of ordinary infectious chorea. In most instances mild or moderately severe movements were noted. Three patients exhibited extremely severe choreic movements. There was frequently more marked involvement of one side than of the other. An akinetic stage was observed in one case. Most of the patients showed psychic changes, such as emotional instability, excitability, lack of insight, impairment of attention and loss of spontaneity. Occasionally indifference or euphoria was observed. The mental alterations often began prior to the movements and frequently persisted after the latter had disappeared. An outspoken psychosis developed in six cases. The symptoms were similar to those of amentia, though mild delirious episodes were common. Acute delirium occurred in one case only. Two patients had albuminuria and intractible vomiting during the first months of pregnancy. The average duration of the disease was four months. In six cases in which pregnancy was artificially terminated, the symptoms disappeared within three days to five weeks. As regards the other patients, recovery took place in the early months of pregnancy in one and during the later months in seven. Nine patients recovered during or shortly after delivery. In four instances the symptoms persisted for from several days to four weeks following childbirth. One patient died after an illness of two weeks' duration. Apart from this, labor occurred spontaneously at term with the delivery of a living child. The illness occurred in subsequent pregnancies in five cases, one patient having three and another four attacks. In general, earlier as well as later pregnancies ran normal courses. Thiele is of the opinion that chorea of pregnancy is identical with Sydenham's chorea. He is inclined to believe that pregnancy acts as a precipitating factor. As to treatment, conservative measures are favored, particularly for patients presenting mild or moderately severe symptoms. Even the outbreak of a symptomatic psychosis is not an absolute indication for the artificial termination of pregnancy, for in four of the six patients showing outspoken psychoses recovery occurred without such intervention.

ROTHSCHILD, Foxborough, Mass.

THE DIAGNOSIS AND LOCALIZATION OF TUMORS OF THE SPINAL CORD BY MEANS OF MEASUREMENTS MADE ON THE X-RAY FILMS OF THE VERTEBRAE, AND THE CORRELATION OF CLINICAL AND X-RAY FINDINGS. CHARLES A. ELSBERG and CORNELIUS G. DYKE, Bull. Neurol. Inst. New York **3**:359 (March) 1934.

The roentgenograms of one hundred normal spines were examined and the interpedicular spaces measured. It was found that such measurements could be made with no more than 1 mm. of inaccuracy, except for the upper three cervical

and the sacral vertebrae. A table of measurements of the interpedicular spaces of the normal spines served as a basis for comparison in the study of cases of tumor of the spinal cord.

The roentgenograms of eighty-six patients with verified intradural and extradural tumors of the spinal cord were then studied with particular reference to an increase in the size of the interpedicular spaces of the vertebrae at the site of the lesion and to variations in the shape of the pedicles. In tumors of the spinal cord it was found that there is often an increase in the size of the vertebral canal at the level of the lesion, which can be recognized only by measurements of the interpedicular spaces. Such enlargement was found in 42 per cent of sixty-seven cases and was more frequently present and more prominent in cases of extradural than of extramedullary growths. The number of intramedullary tumors in this series was too small to warrant conclusions, but in two or three such cases in which a marked enlargement of the spinal cord had been produced there was also a definite increase of the interpedicular space of 2 mm. at the level of the greatest swelling of the cord. In three cases of syringomyelia and in eight cases of adhesions between the membranes the interpedicular spaces were within normal limits.

While the inner borders of the pedicles are usually convex in outline, pedicles with flat inner borders were frequently seen in all parts of the vertebral column. The finding of pedicles with flat inner borders was considered of diagnostic significance only when associated with a measurable increase above the normal in the size of the interpedicular space. The number of vertebrae showing increased interpedicular spacing is considered of importance as indicative of the approximate size of the lesion.

The article contains excellent plates. The authors recognize the need of greater experience in this type of study and also the need of a correlation of the roentgen picture with the clinical findings. They think, however, that these measurements can be accurately and easily made and that they offer valuable aid in the diagnosis and localization of tumors of the spinal cord.

KUBITSCHEK, St. Louis.

INFLUENCE OF CEREBRAL CORTEX ON GASTRO-INTESTINAL MOVEMENTS. J. W. WATTS, J. A. M. A. **104**:355 (Feb. 2) 1935.

Under light ether anesthesia, Watts stimulated various parts of the cortex of the monkey with the faradic current for periods of from one to two minutes, precautions being taken to prevent the spread of the current. With the abdominal cavity open and the intestine floated in warm saline solution, the visceral organs were observed directly. When the premotor area was stimulated, a latent period of about twenty seconds usually elapsed before changes in the gastro-intestinal tract occurred. A marked increase in peristaltic activity of the cecum and the lower part of the small intestine was generally the first change noted, but in some animals striking "peristaltic rushes" were initiated in the colon by such a stimulus. Vigorous peristalsis of the small intestine also occurred, but more often ringlike bands of contraction developed during application of the stimulus, and these as a rule were not transmitted. The persistence of such sharply defined bands of contraction in one segment, aided by peristaltic waves from cephalad segments, resulted in some instances in the invagination of the active portion of the intestine into the lumen of the passive segment lying in continuity with it. Often the intussusceptions so produced were multiple, they were usually formed in the ileum and did not persist permanently, i. e., did not cause obstruction under the conditions of the experiment. Vigorous intestinal movements could be produced by stimulation of many parts of the premotor area, but not from every point within this area. The portion bordering on the superior precentral sulcus, from which Bucy and Fulton obtained ipsilateral movements of the extremities, gave the most consistent increase in intestinal activity. Once activity had been aroused in the intestine by stimulation of the premotor area, faradization of the prefrontal region

and the postcentral gyrus sometimes caused augmentation of activity, but primary stimulation of these regions in the intact cortex were without effect. In one animal from which the premotor area had been extirpated five months previously, stimulation of the prefrontal region and the postcentral gyrus caused a slight increase in peristalsis but never obstruction. In no experiment did stimulation of the motor area influence movements of the intestine. In some experiments stimulation of the cortex caused increased secretion of gastric juice. Bilateral vagotomy abolished most of the cortical responses, though occasionally strong stimulation of the premotor area in such a preparation caused a slight increase in peristalsis. The author states that the experiments described suggest an explanation of the long recognized visceral symptoms and signs associated with focal seizures in man, especially those which occur in the absence of increased intracranial pressure.

EDITOR'S ABSTRACT.

PARALYSIS OF THE LARYNX DUE TO LEAD POISONING: INCLUDING CONTRAINDICATIONS OF "SEMON'S LAW." MERVIN C. MYERSON, Arch. Otolaryng. **20**:659 (Nov.) 1934.

Poisoning due to lead has been known since before the pre-Hippocratic era. Experimental work by Aub and others suggests that fatigued muscles are more prone to become paralyzed as a result of lead poisoning, which suggests that the palsy should occur in the muscles most used, as was suggested by Edinger. It has been demonstrated that distinct lesions occur in the peripheral nerves. If this theory is correct and applies to the laryngeal muscles, the muscles of the larynx most frequently involved should be the adductors. On the basis of what is known of lead paralysis generally, the laryngeal lesions fall into four groups: neuropathic, myopathic, encephalopathic and a combination of neuropathic and myopathic. Myerson finds in the literature reports of twenty cases of plumbism in which the larynx was involved. Early involvement of the larynx has been noted in some cases, but this is not a rule. Lead poisoning has been due to taking snuff, to the use of ferment tablets for making buttermilk, the tablets being placed in a lead glass jar, and exposure to lead from occupation as a printer, painter, potter or typesetter. Myerson reports the case of a man, aged 48, who had lead poisoning with resultant paralysis of the right vocal cord. He died after fifty-three days in the hospital, and the larynx was removed for study.

Semon formulated the theory "that the fibres of the motor nerves going to the abductors succumb to organic affections sooner than or exclusive of the adductors." According to this law the abductor of the vocal cord should succumb much earlier than the adductor. Semon had never seen a case of isolated paralysis of an adductor muscle. Although no histologic studies were made in the series of cases reported from the literature, there is evidence of two cases with unilateral paralysis of the adductor muscle and no other involvement and one case of unilateral paralysis of the adductor muscle associated with involvement of the interarytenoideus muscle. A single case of paralysis of the interarytenoid muscle is included, as are also two cases of bilateral paralysis of the adductor muscle. An unusual case of involvement of both cricothyroid muscles is also included, so that seven of the twenty cases showed involvement of the muscles other than the abductor. These seven, therefore, constitute a definite challenge to the validity of Semon's law.

R. J. HUNTER.

BODY TONUS AND SPACE PERCEPTION. E. FEUCHTWANGER, Arch. f. Psychiat. **100**:439 (Sept.) 1933.

Feuchtwanger describes five cases in which definitely localized injury to the brain led to the development of attacks characterized by disturbances in perception of space. In four the lesions were localized in the frontal lobes, and in one in the cerebellum. In some there were signs of other neurologic disturbances, but

others showed none. The attack began at an interval after the injury and usually showed three phases: 1. The person for a few minutes would have a feeling of a change in his equilibrium, for instance, of his whole body being bent horizontally or vertically in one direction. 2. After the feeling of disturbed equilibrium had passed the patient would become conscious that the outside world had changed in its posture in the opposite direction. Thus, in one case in the second phase the patient perceived the whole outside world as being bent toward the left. This lasted for several minutes, with clear consciousness and insight. 3. A readjustment took place, and the equilibrium of both the person and the outside world became normal. In none of the cases could any disturbance of ocular movements or of hearing be demonstrated. Vestibular disturbances were found in only one case. Feuchtwanger differentiates vestibular disturbances from the condition previously described by the fact that whereas in the former there is usually a feeling of subjective disturbance of equilibrium, in these cases there was also in the second phase a definite feeling of objective disturbance. Furthermore, the vestibular disturbances are usually accompanied by a feeling of movement, whereas in the cases reported here the change in equilibrium was stationary; that is, the change in the outside world was one that remained consistently turned in one direction. During these attacks there were no signs of dizziness, vertigo, nausea or vomiting.

The author discusses a series of cases of similar disturbances that have been reported in the literature, and finds in all that there was no incontrovertible dependence on vestibular lesions. In some cases there were no signs of vestibular disturbance, whereas in others in which such disturbances were present there were also numerous others that could just as well have been the cause of the phenomena. He advances the hypothesis that in the frontal lobe and possibly also in the cerebellum there are special centers that have to do with orientation of the equilibrium of the person himself and of the outside world. These are independent of vestibular function.

MALAMUD, Iowa City.

THE NATURE AND THE NOSOLOGIC AND PATHOGENIC IMPORTANCE OF THE ATYPICAL PROCESSES OF DESTRUCTION IN CASES OF FAMILIAL DISEASES OF THE WHITE MATTER. W. SCHOLZ, Monatschr. f. Psychiat. u. Neurol. **86**:111 (July) 1933.

A study of three cases of familial diffuse sclerosis confirms the view previously expressed by Scholz that the destructive processes occurring in this disorder are atypical. When stained with sudan III or scarlet red, the gliogenous granular cells which take up the products formed by the destruction of the myelinated nerve fibers show a yellow or yellowish-red tint. Typical bright red lipoid material is found only in the cells of the walls of the vessels and in the compound granular corpuscles located in the perivascular spaces. The yellowish prelipoid substance stains deep black with myelin sheath stains, particularly in the early stages. Other diseases leading to destruction of the white matter at first show a similar staining reaction, but the granular cells soon take on only a light smoky gray tint or remain uncolored. In cases of familial diffuse sclerosis, however, the black myelin-like deposits persist for a longer period. Furthermore, similar deposits are found in astrocytes and in the cells of the walls of the vessels. These observations indicate that there is a delay in the process whereby the products of degeneration are converted into lipoid substances that can be absorbed. In one case compound granular corpuscles were not present. Here the astrocytes had proliferated in the form of *gemästete* cells, and the products of destruction were lying for the most part free in the tissues, where they failed to stain with sudan III or scarlet red. There was then a primary insufficiency in the functioning of the glia. There was also an insufficiency of the vascular apparatus, as shown by the almost complete lack of reaction of the elements forming the walls of the vessels. Fatty droplets were not taken up by the adventitial cells to any extent but occurred chiefly as free globules in the adventitial spaces. The inadequacy of the glia, however, was always in the foreground. The microglia and macroglia were equally affected. The similarity of these observations in all cases indicates that the insuf-

ficiency of the glial elements is an essential feature of the disorder. It cannot be secondary, for in other diseases associated with acute and extensive destruction of nerve tissue the phenomena described by Scholz are not encountered. Scholz regards his observations as important because they indicate that the destruction of nerve tissue is not necessarily based on a constitutional weakness or abiotrophy of specific nerve elements but may arise from a disturbance in the function of the glia.

ROTHSCHILD, Foxborough, Mass.

TETANY IN LOCAL ANESTHESIA. HENRY S. WIEDER, Arch. Otolaryng. **18**:155 (Aug.) 1933.

Wieder was accustomed to tell patients to breathe frequently during tonsillectomy under local anesthesia, the idea being that if their attention was held on the breathing they would not gag. He found that this was an excellent way to prevent gagging, but noticed that a number of patients were affected by the procaine hydrochloride. On analysis he decided that this was not due to toxic effect of the drug but was really tetany due to apnea. He noticed an "obstetric" or "penholding" position of the hands, with the fingers straightened and the thumbs adducted, and also tingling of the hands and feet. Wieder has found no other notes in the literature of tetany following tonsillectomy, but cites the experiments of physiologists in eliciting tonic spasms of the hands in normal persons after continued forced breathing for six minutes; these spasms are considered due to alkalosis.

Collip and Backus noted the following changes under the influence of hyperpnea: (1) average fall in the carbon dioxide tension of the alveolar air, 44 per cent; (2) average fall in the carbon dioxide-combining power of the venous plasma, 14.3 per cent; (3) acidity of the urine, markedly decreased; (4) diuresis; (5) rate of elimination of phosphates, increased; (6) rate of ammonia excretion, suppressed; (7) leukocytosis; (8) hyperglycemia; (9) typical symptoms, including tetany; (10) muscle "cramp" and ether spasm possibly due to temporary alkalosis.

Since Wieder has abandoned the technic of having patients breathe rapidly, no further cases have been seen. Of course, anxiety can also produce hyperpnea. He now gives 10 grains (0.65 Gm.) of calcium lactate three times a day for forty-eight hours preceding the operation, together with 1 drachm (3.88 Gm.) of sodium bicarbonate for three nights before retiring, in order to offset the parathyroid deficiency and prevent development of tetany due to hypocalcemia. He discusses the possible effect of the epinephrine used in the anesthetic. It was given in minute doses, but he quote authorities who have found that minute doses act as a synergist in hyperventilation. The author advises that in the future similar cases should be studied for advance signs of tetany, including Trousseau's sign, Chvostek's sign and Hoffmann's sign and that various chemical analyses should be made to study calcium metabolism and alkalosis.

HUNTER, Philadelphia.

CONTRIBUTIONS TO THE HISTOPATHOLOGY OF SCHIZOPHRENIA. B. HECHST, Monatschr. f. Psychiat. u. Neurol. **87**:32 (Oct.) 1933.

Hechst reports the results of a thorough histologic study of the brains of three adults with schizophrenia. The first patient died of hemorrhage from a self-inflicted wound; the second patient was found dead in bed and had a persistent thymus gland; the third patient was very restless, and death followed a sudden collapse. In all three brains there were essentially similar changes. The nerve cells showed sclerosis in some areas and disappearance of Nissl bodies in others. Cell shadows were not uncommon. Slight regressive changes were observed in the oligodendroglia cells and less frequently in the macroglia cells. In a few places progressive glial changes were noted. The oligodendroglia cells were filled with lipoid, and the lipoid content of the nerve cells, particularly those of the third

layer, was distinctly increased. The perivascular spaces contained considerable amounts of fatty material. Cell counts, which were compared with the normal values given by Economo, disclosed a definite loss of nerve cells. Although all layers were affected, the greatest damage occurred in the third lamina, with the fifth, second, sixth and fourth layers showing successively less involvement. The prefrontal area, supramarginal gyrus, angular gyrus and regio parietalis basalis and parts of the first temporal convolution presented the most pronounced alterations, and the area striata, the precentral and postcentral convolutions and the gyri of Heschl, the least. The changes were not always symmetrically distributed in the two hemispheres. Hechst believes that these changes are definitely pathologic and not explainable by fortuitous processes. He was unable to find any noteworthy cerebral lesions in animals killed by sudden exsanguination. Motor unrest, which may lead to circulatory disturbances in the brain, was not noted in the first case. Postmortem influences cannot account for the accumulations of lipoid and glial changes, which undoubtedly took a considerable time to develop. The loss of cells serves as a quantitative measure of the changes and is probably determined by the basic disease process, whereas some of the qualitative alterations may be caused by secondary complicating factors, such as circulatory disturbances. Thus, the subcortical ganglia failed to present loss of cells, though in cases 2 and 3 the corpus striatum showed lesions of cells which were apparently acute and probably bore no direct relation to the schizophrenic disorder.

ROTHSCHILD, Foxborough, Mass.

SYMPATHECTOMY IN ANTERIOR POLIOMYELITIS. E. D. TELFORD and J. S. B. STOPFORD, Brit. M. J. **2**:770 (Oct. 28) 1933.

Patients with anterior poliomyelitis may be much distressed from coldness of the affected limbs, with persistent and severe chilblains, especially during the winter months. An attempt was made to determine why the affected limbs of these patients are blue and cold. It seems that the diminished inflow is a later development and that the primary circulatory defect is impairment of the venous drainage. Observations during operation show that the main arteries to a severely paralyzed limb are much smaller in caliber. Loss of normal stimuli created by activity is responsible for this poor development of the arteries. The loss of muscular activity has also an important effect on the venous return; the blueness and coldness and the liability to chilblains vary directly with the loss of active muscle tissue. When even a small amount of voluntary movement is retained, blueness is not likely to be marked. Telford and Stopford think that the dilatation of the capillaries is secondary to the feeble venous return, plus the possibility of an added factor, namely, the release of histamine, which induces dilatation of the capillaries. Altered trophic influence does not offer a satisfactory explanation. There is no evidence that the sympathetic supply to the vessels of the limb is in any way affected in a typical case of anterior poliomyelitis. If a spinal anesthetic, the effect of which reaches to the sixth dorsal segment, is given to a patient with anterior poliomyelitis of the legs, the lower limbs will show a marked rise in temperature and assume a pink color while the patient is lying down. These observations show that the vasoconstrictor mechanism is intact, because the action of the anesthetic, producing as it does a temporary paralysis of the mechanism, leads to a rise of temperature in a normal limb. Therefore, it seemed evident that if the amount of arterial blood entering a limb affected by anterior poliomyelitis could be increased the coldness and the liability to chilblains would be permanently abolished. Three of the most severe cases were selected, and excision of the lumbar sympathetic ganglia performed. The patients were greatly benefited. During the whole winter the limbs remained warm, and there were no distressing chilblains or incapacity for school or work. The authors think that if ganglionectomy is adequately done, the result is complete and permanent.

FERGUSON, Niagara Falls, N. Y.

POST-ENCEPHALITIC PERSONALITY DISORDERS. E. D. BOND and K. E. APPEL, Ann. Surg. **101**:44 (Jan.) 1935.

Social education, education of the individual person to adjust to society and its customs, is the most important education. It takes the raw impulses of power and domination and transforms them in part into submission and deference. Possessiveness must be partially relinquished and become concession and surrender. Curiosity becomes restrained, and showing off must give place to some degree of modesty. Hate and antagonism must become love and cooperation. This transformation of aboriginal, savage nature cannot be made by emphasizing power, discipline and authority. It can be made by understanding, patience, sympathy and courage. Tyranny, punishment, anger, shame, threats or fear will not accomplish this, for these are the impulses that disorganize society itself, and they certainly disrupt the individual personality.

In cases of encephalitis one meets behavior problems having a substrate origin in organic lesions of the brain. It is important to know how the organic handicap is handled. The community's interest is obvious; these lesions occur in many gifted children whose talents should be saved; the tendencies to antisocial behavior are so great that the community should protect itself. The ordinary family cannot be expected to cope with these difficulties, to give either the physical or the mental care which is demanded. Postencephalitic children are usually too difficult to handle in a foster family. Correctional institutions only make matters worse. The community must come forward with hospitals and camps. To reeducate these children it should furnish highly trained teachers and social workers, special diagnostic centers and special schools with classes limited to fifteen pupils, with the right to exclude the feebleminded, and as a last resource it should maintain a boarding school under psychiatric auspices. This plan is difficult and expensive, but it is easier and less expensive than no plan at all. Care under such a community plan will prevent the disorganization of families and neighborhoods, will prevent the development of some criminals, will save many talented children and will offer many suggestions for the better education of all difficult or unusual children.

GRANT, Philadelphia.

THE ACTION OF AN ESTROGENIC SUBSTANCE ON THE INTERSTITIAL GLAND OF THE OVARY. CONSTANCE PARHON-STEFANESCU, Rev. franç. d'endocrinol. **12**:225 (June) 1934.

This study is an elaboration of previous observations on the effects of the administration of a glandular extract on the corresponding gland in the animal. Peiser, Utterstroem and others noted decrease in the volume of the thyroid gland in animals in which hyperthyroidism was produced by the administration of thyroid extract. Similar observations were made by Leriche, Jung and Sureyya on the administration of parathyroid extract. Del Castillo and Calatroni found no ripe follicles or recently developed corpora lutea in normal rats treated for a long period with an estrogenic substance. Proceeding along these lines, Parhon-Stefanescu examined the ovaries of two bitches, aged 1 month, one of which was given injections twice daily of 50 units of an estrogenic substance for twenty-seven consecutive days, while the other was kept as a control. Sudan III and hematoxylin stains were used. Parhon-Stefanescu found the interstitial gland in the control animal better developed, showing a large number of cellular groups in the microscopic field with a greater number of cells in each group. There was, however, no appreciable difference in the graafian follicles in the two animals, only primordial or immature follicles being present in the ovaries of both (probably due to the early age of the animals). The genital tract of the treated animal was increased in volume and much congested in comparison with the tract in the control animal. Parhon-Stefanescu also injected 25 units twice daily for thirty-four days into a guinea-pig weighing 180 Gm. The genital tract of this animal was much larger than that in the control animal of the same weight. Histologic examination showed a better developed thecal gland in the control animal but no change

in the graafian follicles. The author thinks, therefore, that prolonged administration of an estrogenic substance prevents the development of the interstitial and thecal glands in the ovary, thus substantiating the observations previously made by other workers concerning the reduction of the activity of an internal gland when a corresponding extract is introduced into the organism from without.

NOTKIN, Poughkeepsie, N. Y.

STABILIZATION OF BLOOD PLASMA DURING PROTRACTED NARCOSIS WITH A BARBITAL DERIVATIVE. S. SCHRIJVER-HERTZBERGER and D. SCHRIJVER, Acta psychiat. et neurol. **9**:149; 1934.

The favorable therapeutic results obtained in patients suffering with a schizophrenic psychosis after they have been submitted to a protracted narcosis with a barbital derivative manifest themselves not only in the psychic sphere but also by somatic changes. One of these changes is the greater colloidal stability of the plasma. Schrijver-Hertzberger and Schrijver have studied this phenomenon with a method of their own: Four volumes of blood are added to one volume of 3.6 per cent solution of sodium citrate and the mixture is centrifugated. The plasma is distributed in a series of test tubes in quantities of 0.5, 0.4, 0.3, 0.2 and 0.1 cc., respectively. To each tube physiologic solution of sodium chloride is added in quantities of 0, 0.1, 0.2, 0.3 and 0.4 cc., respectively. After the saline solution and blood are mixed, 0.5 cc. of saturated solution of sodium chloride is added to each tube. After standing for one hour the precipitation in each tube is observed and recorded. The labile plasma gives precipitation in all tubes, and thus the reaction is recorded as 5. The stable plasma gives no precipitation in any or only in the first two tubes. These results are recorded as 0, 1 or 2, according to the occurrence of precipitation in the series of tubes. The authors found that in general the plasma of patients who responded favorably to the treatment with protracted narcosis showed a certain degree of stability. This stabilization of plasma was manifest either during the period of narcosis or after it. On the contrary, the plasma of patients who did not respond well to the treatment showed no such stability, the precipitation occurring in the first three or four tubes; or even in all five. The authors discuss the colloidal mechanism and the general implications of this phenomenon.

YAKOVLEV, Palmer, Mass.

BILATERAL FIRST THORACIC GANGLIONECTOMY IN TWO CASES OF PARKINSON'S SYNDROME. GORDON HARROWER and K. C. GHOSH, Brit. M. J. **2**:772 (Oct. 28) 1933.

The first case reported appeared to be one of Parkinson's syndrome following encephalitis involving all four extremities, the tongue, the lips, etc.; cerebration was extremely slow. The first thoracic sympathetic ganglion on the right side and the last cervical ganglion, which was fused to it, were removed, and nine days later the operation was repeated on the left side. There seemed to be slight improvement in the tremors and a fairly pronounced change in the mental attitude of the patient.

The second case was one of unilateral Parkinson's syndrome, also apparently the result of encephalitis. The first thoracic ganglion on the right was removed, and nine days later the operation was repeated on the left side. The patient's mental outlook and disposition were slightly better, but no notable improvement was observed in the muscular condition. Thus, as a therapeutic measure, this procedure is questionable. Observation of the function of the heart in these cases is of extreme interest. It appears that sympathetic control of the heart is not essential for normal function. Stimulation of the sympathetic nerve supply produces an increase in the heart rate. In several cases the vagus nerve was accidently sectioned in the neck on one side, with no appreciable difference in the action of the heart. Such results lead one to believe that the rate of the pulse is dependent primarily on the intrinsic plexuses and that the vagus and the sympathetic innervation merely exercise a controlling influence on the heart in mental states such as

excitement and depression. If this is not so, there must be sympathetic and parasympathetic fibers reaching the heart from sources as yet unknown.

FERGUSON, Niagara Falls, N. Y.

UPPER MOTOR NEURON LESIONS: ANALYSIS OF SYNDROMES OF MOTOR AND PREMOTOR AREAS. J. F. FULTON and H. R. VIETS, J. A. M. A. **104**:357 (Feb. 2) 1935.

Fulton and Viets believe that paralysis of voluntary movement may be due to lesions of either the upper or the lower motor neuron. The manifestations of lesions of the lower motor neuron are identical with those following section of a motor nerve. Manifestations of paralysis of the upper motor neuron are various, and in the past no attempt has been made to dissociate the symptoms produced by destruction of the pyramidal pathways from those produced by interruption of other voluntary projection systems from the cortex. Recent studies on the specific components of lesions of the upper motor neuron in monkeys, apes and man allow the following conclusions: 1. Lesions restricted to the pyramidal tracts or to their cells of origin cause flaccid motor paralysis, muscle atrophy, transient depression of all reflexes and the positive signs of Babinski and Chaddock; after complete destruction of the pyramids, the signs of Babinski and Chaddock persist permanently, but the paralysis, flaccidity and reflex changes tend to disappear with time. 2. Lesions of the premotor projection area of the cortex, which also mediate voluntary movements, give rise to spastic paralysis, disturbance of skilled movements, forced grasping, vasomotor disturbances, increased deep reflexes and the signs of Rossolimo, Mendel-Bechterew and Hoffmann. Forced grasping and vasomotor disturbances are transient, but disturbance of skilled movements and the signs of Rossolimo and Hoffmann tend to persist. 3. Hemiplegia in man is generally produced by combined destruction of motor and premotor components of the upper motor neuron, and hence such cases generally exhibit combinations of the foregoing symptoms with more severe ultimate motor paralysis than when only the pyramidal tracts are involved. The prognosis can be inferred from the extent to which the two systems are involved.

EDITOR'S ABSTRACT.

THE CLINICAL FEATURES OF PSYCHOSES DUE TO HASHISH. M. G. STRINGARIS, Arch. f. Psychiat. **100**:522 (Sept.) 1933.

Stringaris had an opportunity to study a large number of persons in Greece who were addicted to the use of hashish, this type of drug addiction apparently being common in that country. He found that addiction to the drug predisposes to the formation of groups, the addicts rarely using it in solitude. Chronic addiction is particularly frequent in persons who begin to use the drug before the eighteenth year of life. Persons of a roaming, shiftless type are particularly apt to become addicted to it. Acute intoxication is characterized by euphoria, increased motor activity, excitability, talkativeness, laughter and appetite. Hallucinatory and delusional experiences are frequent. Occasionally, especially in persons who suffer from chronic addiction, depression instead of euphoria will occur. Chronic use of the drug leads to definite changes of personality. There are decrease in judgment and hyperirritability, with childish outbursts of anger and assaultiveness. There is gradually increasing suspiciousness and paranoid attitude, with a pronounced increase in sexual excitement. Occasionally definite psychoses occur; the author classifies these into two groups: (1) episodic psychoses, which may take the form of hallucinatory or acute twilight conditions, with excitability and furor; (2) the chronic type, which may last for months or even years and follow prolonged use of the drug. The symptoms are not unlike those in cases of schizophrenia, with bizarre hallucinations and delusions, impulsive and compulsive phenomena, paranoid formations, fear reactions, etc. Differentiation between them and transitory schizophrenic episodes is difficult, and it is questionable whether such psychoses do not develop primarily in schizoid personalities, the drug acting mainly as a precipitating agent.

MALAMUD, Iowa City.

THE SYMPTOMATOLOGY OF VENTRICULAR HEMORRHAGE. H. STRAUSS, Monatschr. f. Psychiat. u. Neurol. **85**:1 (Feb.) 1933.

Ventricular hemorrhage may be primary or secondary. In the former the loss of blood is from a vessel situated in the ventricular system; in the latter blood extravasated in the brain substance breaks into the ventricles. Reports of primary ventricular hemorrhage are relatively rare in recent literature. Strauss reports fourteen cases, in one of which the hemorrhage was primary. His own observations, taken in conjunction with those recorded by others, lead him to emphasize the following features: unconsciousness or clouding of consciousness; tonic convulsive attacks, often with the appearance of tonic reflexes of the neck; various types of rigidity, such as decerebrate rigidity or hypertonic states with abnormal postures; tremors; myoclonic phenomena; grasping reflexes, and iterative motor unrest in which complicated movements may be performed. There may be disturbances of the pupils or of the external ocular muscles. Vomiting at the onset, vasomotor changes and abnormalities of temperature are common. Most of the symptoms are caused by direct damage to structures in the brain stem or by the pressure of the extravasated blood on these structures. The iterative motor unrest arises from involvement of the caudate nuclei. Decerebrate rigidity is based on injury of the function of the red nucleus produced by increased pressure within the third ventricle. In secondary ventricular hemorrhage Strauss frequently observed a syndrome characterized by unconsciousness, tonic convulsive attacks resembling attacks of decerebrate rigidity and paralysis of one side with grasping movements and other iterative movements on the other side.

ROTHSCHILD, Foxborough, Mass.

MENINGIOMA AS A CAUSE OF EPILEPSY. R. A. GROFF, Ann. Surg. **101**:167 (Jan.) 1935.

In a series of 291 cases of meningioma epilepsy occurred in 30.9 per cent, or in 90 cases. Among these 90 cases, there were 18 of grand mal, 7 of petit mal and 65 of jacksonian seizures. The last group was divided into 36 cases of a motor type of attacks, 22 of sensorimotor spells and 7 of pure sensory seizures. Aside from these 90 cases, there were 12 cases of uncinate fits.

In 14 of the 18 cases of generalized convulsions the lesions were in the frontal or temporal lobes or arose from the sphenoid ridge. Fifty-four of the 65 cases of jacksonian epilepsy were due to tumors involving the frontal and parietal lobes. Ten of the 12 cases of uncinate fits were due to tumors in close relationship to the uncinate gyrus.

The incidence of epileptic seizure was greatest in tumors compressing the frontal, parietal and temporal lobes. There were 116 patients with tumors in this region, and 80 had convulsions. All except 16 of these had focal attacks. In the 21 cases of tumor located in the posterior fossa, not 1 was complicated by convulsive seizures.

Sixty-six patients had preoperative convulsions. Twenty-four were relieved after removal of the tumor in an average follow-up period of four years. Thirteen of the 201 patients without convulsions had seizures after operation. Eight of these had jacksonian seizures, while the remaining 5 had grand mal attacks.

GRANT, Philadelphia.

THE MIGRAINOUS PATIENT. GRACE A. TOURAINE and GEORGE DRAPER, J. Nerv. & Ment. Dis. **80**:183 (Aug.) 1934.

Touraine and Draper have described a characteristic constitutional type for the person with migraine, consisting of an acromegalic skull, outstanding intelligence and emotional retardation. Each attack of headache is characteristic of the patient, follows the same pattern and recurs in similar circumstances. Situations involving the loss of home protection, a necessity for the person to stand alone, to grow up, and the advent of personal adult responsibility mark the moment in life when the

headaches first appear. There is an evident familial predisposition to migrainous headaches. The character of the attack is often similar in the several afflicted members of a family group. In most cases the headaches come through the maternal line. The factor of unwitting imitation of the migrainous ancestor appears to be an important aspect of the genetic interpretation. A satisfactory sexual adjustment is not found, for there seems to be an arrest at some point in the psychosexual development. The authors, however, think that the problem is far from solved. The psychic mechanism most often found seems to be in conflict between the desire to escape from the mother's influence and a compulsion not to leave her. It seems as if part of the total personality were separated from the person himself and caught in the maternal attachment. The authors consider the migraine attack as comparable to any other neurosis. The physiologic processes which cause the headache are secondary to the emotional discharge from the aforementioned conflict.

HART, Greenwich, Conn.

CALCIUM CONTENT OF THE AQUEOUS AND VITREOUS HUMORS AND SERUM. PETER W. SALIT, J. Biol. Chem. **104**:275 (Feb.) 1934.

Comparative studies were made on the calcium content of the aqueous humor, vitreous humor and serum of cattle in an effort to determine the distribution with respect to age. The animals were roughly classed into three groups: young calves, from 4 to 8 weeks old; young adult cattle, from 1 to 2 years old, and older animals, from 5 to 10 years old. Young calves have the highest concentration of calcium in all three fluids, averaging 5.82, 8.34 and 11.54 mg. per hundred cubic centimeters in the aqueous humor, vitreous humor and serum, respectively. In young adult cattle the averages for these three fluids were 5.42, 7.17 and 10.32 mg., and in aged cattle, 4.60, 6.75 and 9.69, respectively. The calcium content of the vitreous humor exceeded that of the aqueous humor in all groups. If the enucleated eyes were allowed to stand the calcium content of the aqueous humor approached that of the vitreous humor, the semipermeable membrane becoming more permeable after death. The ratios of the calcium content of the vitreous humor and of the aqueous humor to that of the serum indicate that the calcium content of the ocular humors is directly dependent on the calcium content of the serum. It is interesting that the calcium content of the vitreous humor more closely resembles that of body fluids with a high protein content, whereas the aqueous humor, with a low protein content, has a calcium content approximately 50 per cent of the serum calcium, which is what has been found in cerebrospinal fluid.

DAILEY IRVINE, Boston.

UNILATERAL BLINDNESS: LATENT CLOSED EMPYEMA OF A POSTERIOR ETHMOID CELL; RECOVERY FOLLOWING OPERATION. L. CERISE, J. RAMADIER and H. GUILLON, Rev. d'oto-neuro-opht. **12**:499 (July-Aug.) 1934.

A man, aged 32, entered the hospital with the complaint of loss of vision in the left eye and periorbital pain for the previous eight days. Examination revealed a slightly swollen and edematous papilla and an enormous central scotoma in the left eye. Vision was limited to a narrow crescentic area with its concavity downward. There was no sign of nasal suppuration, and the roentgenographic examination showed no evidence of involvement of the sinuses. Since the vision rapidly diminished to complete blindness, resection of the septum and exploration of the posterior sinuses were done. Two cubic centimeters of thick, fetid pus was evacuated from a posterior ethmoid cell. The operation was not extended farther. Improvement was immediate, and at the end of the eighth day the visual field and the papilla were normal, and vision was 9/10. From an ophthalmologic point of view, this case was one of optic neuritis with functional signs quite different from the classic form. The authors agree with Portmann and Pesme that the association of functional signs of retrobulbar neuritis with papillary lesions and painful symp-

toms suggests that these ocular disturbances originate from an infected sinus. In such cases, even when the nasal examination gives negative results, an early exploratory operation on the ethmoid and sphenoid sinuses is indicated.

DENNIS, San Diego, Calif.

THE CELLS OF THE CEREBROSPINAL FLUID. A. BANNWARTH, Arch. f. Psychiat. **100**:533 (Oct.) 1933.

Examination of the type and nature of the cells in the cerebrospinal fluid can best be carried out by one of the following two methods: (1) the French method, in which the fluid is centrifugated and the smear made from the sediment is stained by the Leishman method; (2) the histologic method devised by Alzheimer, in which the cells are precipitated with the aid of albumin and the coagulum formed is embedded in pyroxylin, sectioned and then stained either with the Nissl stain or by the Pappenheim method. Of the two, the histologic method is to be preferred, as it affords a clearer picture. It was found that the cells in the cerebrospinal fluid usually show degenerative changes which indicate that during their presence in the cerebrospinal fluid they are subjected to injurious influences. This was substantiated by the fact that injections into the thecal canal of substances that produce aseptic meningitis brought out cells of a comparatively intact type. Pleocytosis is most frequent in cases in which the leptomeninges are affected, but it may also occur when no disease of the meninges exists but the vessels of the brain substance are disturbed. From his observations Bannwarth concludes that the cells in the cerebrospinal fluid come from the connective tissue mainly; only a few of them are of hematogenous origin.

MALAMUD, Iowa City.

SPECIFIC TREATMENT FOR SYPHILIS AND THE INCUBATION PERIOD (LATENT PERIOD) OF DEMENTIA PARALYTICA AND TABES. P. JOSSMANN, Monatschr. f. Psychiat. u. Neurol. **84**:245 (Dec.) 1932.

Jossmann investigated 734 cases of dementia paralytica and 908 cases of tabes with regard to the relation between the treatment given and the duration of the latent period. He confirmed the frequently stated opinion that with increasing age the period of latency tends to become shorter. This was taken into account in compiling his statistics. All patients were of the male sex. In the great majority of instances mercury was the only drug used. In general, patients who had not been treated showed the longest period between the date of infection and the onset of the neurosyphilis. In the cases in which treatment had been given there was a slight but definite shortening of the latent period. This was greatest in patients receiving the most intensive therapy. However, Jossmann believes that the vast majority of patients had been given insufficient treatment. He therefore concludes that such inadequate therapy is more harmful than complete lack of treatment. A group of 56 patients who had received arsphenamine chiefly or exclusively showed somewhat different results. While the number of cases was too small to warrant reliable conclusions, it was thought that the intensive use of arsphenamine tended to prolong the length of the latent period.

ROTHSCHILD, Foxborough, Mass.

THYMOPATHIC DEPRESSIONS OF MOOD IN EPILEPTIC PATIENTS. K. VOLLAND, Arch. f. Psychiat. **100**:670 (Oct.) 1933.

A certain number of patients with epilepsy, either idiopathic or traumatic, have disturbances of mood which are mostly in the nature of depressions but occasionally also attacks of manic excitement. Certain features distinguish these epileptic persons from others. In their ancestry one finds a heavy preponderance of disturbances of mood and cyclothymic personalities, with very few cases of epilepsy. The premorbid personality shows definite cyclothymic features. In some, manic-depressive attacks precede the occurrence of the epileptic convulsions. The course of the

disease is also distinctive in that few of the patients show any signs of intellectual deterioration even when the disease has been of long standing. In some, the epileptic convulsions disappear after a number of years leaving the type of personality that is usual in manic-depressive persons. None of the features characteristic of the epileptic personality, such as egocentricity, stickiness, monotony and explosive reactions, could be found in any of these patients. The swings of mood may occur either preceding or following an epileptic attack, or may take place without any relationship to an attack. The prognosis is usually good, although in the cases in which depressions occur suicidal attempts are frequent.

MALAMUD, Iowa City.

THE NOT UNFAVORABLE COURSE OF AMNESIC AND POLYNEURITIC ALCOHOLIC PSYCHOSES. H. SIEBERT, Monatschr. f. Psychiat. u. Neurol. **82**:217 (Aug.) 1932.

Fifty-seven cases of alcoholic psychosis of an amnesic-polyneuritic type were observed by Siebert. Cases in which there were accessory factors, such as renal disorders, arteriosclerosis, acute infection or trauma, were excluded. The average age for the group fell within the fifth decade of life. All patients had for many years been habitual drinkers of beverages with a high alcoholic content. In thirty-one cases the outcome was favorable as regards symptoms of mental disorder. In these cases the discrepancy between the retention of new impressions and memory for remote events disappeared, confabulations ceased to occur and the ability to work was regained. There was no constant parallelism between the physical changes and the psychotic manifestations, one group of symptoms sometimes improving without corresponding improvement of the other. Confabulations were suggestive of a poor prognosis, especially when they continued for a considerable period of time. Siebert found that a radical change of environment with change of occupation was of benefit in his cases.

ROTHSCHILD, Foxborough, Mass.

UTILIZATION OF BAILLIART'S METHOD OF DIAGNOSING INTRACRANIAL HYPERTENSION OCCURRING AFTER RECENT CRANIAL TRAUMATISM. A. ARNAUD and P. GUILLOT, Ann. d'ocul. **171**: 735 (Sept.) 1934.

Arnaud and Guillot report seven cases of intracranial hypertension occurring after traumatism. The study of these cases indicates to the authors that the ophthalmologist has an important rôle in the clinical study of cranial traumatism. However, it is understood that the ophthalmologist's opinion is valuable only when he may indicate the possibility of intracranial hypertension. Therefore, the ophthalmotonometer or dynamometer is used when operation is indicated because of suspected intracranial hypertension. The clinical symptoms permit the diagnosis of diffuse intradural hematoma, peribulbar effusion, intraventricular blocking, etc. Lenormant and Wertheimer believe that these symptoms are of great value. In cases in which marked hypertension exists, absence of ocular signs indicates nothing in regard to treatment. Arnaud and Guillot believe that the complete study of intracranial hypertension does not exclude clinical and manometric examinations. These tests are supplementary and are of benefit in cases in which increased intracranial tension is suspected.

BERENS, New York.

PSYCHOSES ASSOCIATED WITH PERNICIOUS ANEMIA. D. M. PROFITT, J. Neurol. & Psychopath. **15**:12 (July) 1934.

The first of two cases reported occurred in a single woman, aged 33, who was depressed, apathetic, retarded and mildly confused. She heard hallucinatory voices and had ideas of unworthiness and delusions of danger concerning her father. The blood picture was fairly typical, and the gastric juice showed a free acid response to histamine, which the author admits is sufficiently rare to cause the

diagnosis to be questioned. Cellulitis developed shortly after the patient was admitted and disappeared after several weeks. The second case was that of a man, aged 57, who presented a fairly typical Korsakoff syndrome. There was a definite history of alcoholism, and the blood picture showed a severe degree of anemia. In both cases improvement in the mental status was correlated with that of the blood; this was well illustrated by the case of the first patient, who had a remission during observation. These two cases support the view that mental changes developing in persons with pernicious anemia depend on the state of the psyche at the time the disease develops.

SPERLING, Philadelphia.

TUBERCULOUS MENINGITIS IN ADULTS. A. H. HOLMES, Lancet **2**:639 (Sept. 16) 1933.

Although the literature concerning tuberculous meningitis is vast, the data accumulated have dealt to a large extent with the manifestation of this disease in children. In this series, twenty-nine cases of proved tuberculous meningitis in patients over 15 years of age are reviewed. The sexes were equally represented, and the average age was 26. The average duration of illness was fourteen and one-half days, with no instance of recovery. All the classic signs and symptoms, as found in children, show great variation in prevalence, in intensity and in the time of their appearance; many may be absent throughout the illness. A clinical diagnosis of meningitis in adults is rarely possible before the tenth day; an etiologic diagnosis is possible only by the finding of tubercle bacilli in the cerebrospinal fluid, although tuberculosis is suggested by the presence of coagulum and lymphocytosis and an increase in the protein content and a decrease in the chloride content. The most useful clinical signs are those relative to the neck, the eyes and the pyramidal tract.

BECK, Buffalo.

THE DETERMINATION OF PERSONAL INTERESTS BY PSYCHOLOGICAL AND GRAPHOLOGICAL METHODS. H. CANTRIL, H. A. RAND and G. W. ALLPORT, Character & Personality **2**:134 (Dec.) 1933.

Fifty subjects were scored for esthetic, theoretical, economic, political and religious interest according to the "Study of Values" by P. E. Vernon and G. W. Allport. A graphologist, from a study of samples of handwriting, rated the same subjects on these five dispositions of personality. The scores obtained in these two ways were reduced to standard measures. The graphologic and the psychologic estimates in respect to each value gave the following coefficients of correlation: aesthetic, 0.4 $\pm$ 0.08; economic, 0.29 $\pm$ 0.09; theoretical, 0.25 $\pm$ 0.09; political, 0.07 $\pm$ 0.10, and religious, — 0.06 $\pm$ 0.10. Combining the five separate series of data into a single correlation, the coefficient becomes 0.21 $\pm$ 0.04. The authors believe that the agreement between psychologic and graphologic psychodiagnosis will increase with improvements in methods of research and that such agreement as has already been discovered is evidence that each must be to some degree correct.

MATHER, Howard, R. I.

LINGUAL SPASM. S. COBB and J. MIXTER, Ann. Surg. **101**:49 (Jan.) 1935.

A case of atypical neuralgia of the trigeminal nerve is described in which lingual spasms appeared after the sensory trigeminal nerve had been cut. The lingual branch had atrophied, but the autonomic branch from the geniculate ganglion of the facial nerve joins the lingual nerve peripheral to the site of the neurotomy. The lingual nerve, therefore, functionally remained only as a vasodilator to the tongue. The motor innervation to the tongue was intact. The spasms were associated with vasodilatation of one half of the tongue and ceased after section of the lingual nerve. Vulpian and Heidenhain showed that section of the motor nerve to the tongue caused paralysis and atrophy but that stimula-

tion of the lingual nerve, which contains at that point the parasympathetic fibers of the chorda tympani, caused a slow contracture of the tongue. These movements came on after a long latent period. They were observed in the tongue only after partial degeneration of the hypoglossal nerve had taken place. This spasm may be relieved by cutting the chorda tympani fibers in the lingual nerve.

GRANT, Philadelphia.

TREATMENT OF PATIENTS WITH DEPRESSIVE STATES WITH SEX HORMONES. PAOLO JEDLOWSKI, Arch. gen. di neurol., psichiat. e psicoanal. **14**:41, 1933.

Psychoses of the depressive type are favorably influenced by the hypodermic administration of extracts of sex organs of lower vertebrates (birds and fishes). Apart from the complete subsidence of psychic symptoms which sometimes occurs, there usually is also an improvement of the general condition, with a gain in weight in some cases of from 10 to 11 Kg. in a period of from one to three months. Intravenous injections of the extracts are more efficacious than intramuscular injections; in all cases the treatment must be continued for some time after apparent recovery. The good results are obtained regardless of whether homonymous or heteronymous extracts are used. However, in some cases the extracts of heteronymous (opposite) sex organs prove to be more efficacious. This tends to show that the action of such extracts is not simply substitutive. The treatment with sex hormones, while giving excellent results in patients with depressive psychoses, is ineffective or even dangerous in excited patients.

YAKOVLEV, Palmer, Mass.

TREATMENT OF CHOREA BY INDUCED PYREXIA. J. W. CHEETHAM, Brit. M. J. **2**:815 (Nov. 4) 1933.

The present aim of treatment in cases of Sydenham's chorea may be summarized in a single word—rest. The heart is involved in such a high proportion of cases (50 per cent) that a minimum of three months' rest in bed has been arbitrarily fixed in all cases, whether or not there is clinical evidence of carditis. The question whether treatment of chorea by pyrexia has a bad effect on the heart has been given special consideration in this article. The conclusions drawn are: artificial pyrexia shortens the duration of choreic movements; it does not prevent recurrence, and it appears to have no beneficial action on rheumatic carditis. Its grave danger lies in the tendency to produce a false impression of cure by abolishing the movements, which in themselves are merely a symptom, when serious changes may be occurring in the heart. With these facts in mind, it seems that the use of artificial pyrexia has a limited place in the treatment for chorea.

FERGUSON, Niagara Falls, N. Y.

TREATMENT OF CHOREA BY INDUCED PYREXIA. HUXLEY FISH, Brit. M. J. **2**:816 (Nov. 4) 1933.

A case of chorea is reported in which artificial pyrexia was induced. The duration of the chorea was cut short. The method has definite disadvantages, of which the most obvious is the discomfort it causes the patient. Also, there is a risk of the temperature becoming so high that the patient's life is endangered. The fact that slight dilatation of the heart occurred makes one chary of applying the treatment to any person with well marked valvular disease. Fish tentatively suggests patients with the following types of chorea as suitable for treatment by this measure: (1) patients with no signs of cardiac rheumatism, who show little improvement after four weeks in bed in an institution; (2) patients with slight cardiac rheumatism, and (3) patients with choreic relapse, in whom the previous attack or attacks have been of long duration (the heart again being only slightly affected).

FERGUSON, Niagara Falls, N. Y.

FAMILIAL GLIOMA (THE GENETICS OF GLIOMA). W. BENDER and F. PANSE, Monatschr. f. Psychiat. u. Neurol. **83**:253 (Sept.) 1932.

Bender and Panse report the occurrence of symptoms pointing to tumor of the brain in three brothers. Postmortem examination, which was performed in one case, revealed a glioma involving the central portions of the brain. Microscopically the tumor was rich in polymorphous and mitotic cell forms. It was regarded as belonging in the group of spongioblastoma. Histologic examination of the cerebral cortex disclosed developmental anomalies of the cyto-architecture. One of the patients observed by the authors presented a tumor of the skin which resembled adenoma sebaceum and the others showed nevi. These features lead Bender and Panse to conclude that familial glioma and tuberous sclerosis are closely related. They believe that their cases belong in the group designated by Bielschowsky as fetal spongioblastosis, which includes tuberous sclerosis, Recklinghausen's disease, familial hypertrophic neuritis and probably certain forms of epilepsy and diffuse sclerosis.

ROTHSCHILD, Foxborough, Mass.

THE FUNCTIONS AND STRUCTURE OF THE NEURAXIS IN REGARD TO VOLUNTARY AND REFLEX MOVEMENTS. S. D. INGHAM, Ann. Surg. **101**:184 (Jan.) 1935.

On a basis of anatomy, physiology, pathology and clinical observations, a hypothesis is presented to explain facts concerning the motor mechanisms which are not comprehensible on the basis of only an upper and a lower motor neuron. In brief, the hypothesis suggested is that the main connection of the upper motor neuron is not direct with the lower motor neuron but through an intercalated system of neurons which acts as a correlating and distributing mechanism for voluntary and reflex motor impulses. This mechanism forms a system of patterns throughout the brain stem and the spinal cord. Anatomically, the system consists of fiber tracts such as the posterior longitudinal bundle and the reticulospinal tract. The substantia reticularis of the brain stem and the spinal cord and the fasciculus proprius of the spinal cord probably constitute part of this system.

GRANT, Philadelphia.

TOLOSA'S SIGN AND VISCERAL SENSIBILITY IN CASES OF TABES. J. DA FONSECA BICUDO JR., Rev. Assoc. paulista de med. **4**:78 (Feb.) 1934.

Da Fonseca Bicudo Jr. distinguishes two cremasteric reflexes, the deep and the superficial. He gives the name of Tolosa's sign to the disappearance of one cremasteric reflex with conservation of the other. The first variety of the sign is that in which the deep reflex has disappeared and the superficial reflex is present, and the second variety, that in which the superficial reflex has disappeared and the deep reflex is present. The author found that in cases of tabes the deep cremasteric reflex frequently disappears while the superficial reflex is present (first variety of the Tolosa sign). In no case did he find the second variety of the sign. The deep cremasteric reflex is intimately related to visceral sensitivity. The determination of both the superficial and the deep cremasteric reflexes is of importance in neurologic examinations, since the first reflex gives one information concerning tactile sensibility and the second reflex, information concerning visceral sensitivity.

EDITOR'S ABSTRACT.

INTRACRANIAL OPERATIONS IN THE SITTING POSITION. W. J. GARDNER, Ann. Surg. **101**:138 (Jan.) 1935.

The sitting position of the patient, combined with avertin anesthesia, is recommended for operations on the cerebellum. This position results in a diminution in bleeding, a lowering of intracranial pressure, a lessened tendency to immediate cerebral edema and improved respiratory exchange, and it also facilitates access to the patient, particularly by the anesthetist. This position is not recommended for operations on tumors about the sella turcica or on the inferior surfaces of

the cerebral hemispheres. In other cerebral tumors the position is recommended with reservation because of the tendency for an occasional patient to pass into prompt and profound shock. The position has distinct advantages in laminectomy on the cervical and upper dorsal vertebrae and in excision of the cervicodorsal sympathetic ganglia by the Adson approach. It does not predispose to postoperative hemorrhage.

GRANT, Philadelphia.

TROPHIC CHANGES OF JOINTS IN POSTENCEPHALITIC PARKINSONISM. LELIO GRIMALDI, Arch. gen. di neurol., psichiat. e psicoanal. **15**:105, 1933.

Grimaldi reports deformities of the phalangeal joints of both hands and one foot in a case of postencephalitic parkinsonism. Roentgenographic study of the affected joints revealed atrophic changes in the cartilages and epiphyses. The author regards these changes as neurotrophic and as having relation to the lesions of the diencephalon. He reviews the literature on the subject of deformities of the joints in various diseases of the diencephalic region and points out that cases reported in the literature, including his own, reveal common clinical pictures while the localization of the neurotrophic changes differ (tendons, ligaments, cartilage, periosteum and bone). He considers these variations in relation to the participation of the endocrine apparatus in the mechanism of the pathologic process.

YAKOVLEV, Palmer, Mass.

INTRACRANIAL HYDRODYNAMICS. JULES H. MASSERMAN, J. Nerv. & Ment. Dis. **80**:138 (Aug.) 1934.

Rapid lumbar drainage of cerebrospinal fluid can cause herniation of the cerebellum into the foramen magnum only under certain conditions. Rapid decompression of the tension of the intracranial fluid, especially if the latter is increased, results in trauma to the central nervous system and subsequent edema. These pathologic changes are at the basis of many of the untoward effects following rapid drainage of the spinal fluid for diagnostic, therapeutic or roentgenologic purposes. The incidence of untoward postpuncture symptomatology may therefore be reduced by gradual decompression of the spinal fluid at the time of drainage. Further, the postdecompressive syndrome, once established, may best be alleviated by measures indicated for the relief of shock and edema of the central nervous system.

HART, Greenwich, Conn.

A WARNING REGARDING BASAL NARCOTICS. R. J. MCNEILL LOVE, Brit. M. J. **1**:327 (Feb. 24) 1934.

Two cases are reported in which narcotics were undoubtedly a contributory cause of death. It appears that it is extremely unwise to administer morphine or omnopon in conjunction with basal narcotics. Love administers avertin only in amounts corresponding to two thirds of the official dose and supplements its effects with gas and oxygen as necessary. Treatment of narcotic poisoning consists in the administration of cardiac stimulants, intravenous infusions of solution of sodium chloride and dextrose (5 per cent) and inhalations of oxygen. Repeated lumbar punctures are valuable. Frequent injections of strychnine have given good results in some cases. In a case of barbital poisoning not less than 6 grains (0.4 Gm.) of strychnine was administered in sixty hours; recovery ensued.

FERGUSON, Niagara Falls, N. Y.

VASCULAR CHANGES IN CASES OF MUSCULAR DYSTROPHY. K. MÉSZÁROS, Monatschr. f. Psychiat. u. Neurol. **87**:180 (Nov.) 1933.

A study of the peripheral vascular system in ten cases of progressive muscular dystrophy disclosed outspoken abnormalities. Capillaroscopy revealed morphologic changes of the capillary vessels and a slowing of the blood flow. All but one of

eight patients tested by producing artificial anemia of a finger showed a delay in the restoration of normal circulation. The changes point to a definite retardation of vascular development and a high grade disorder of function, which are probably based on disturbances of the autonomic nervous system. It is possible that the anatomic and functional alterations of the small vessels play a rôle in the metabolic disturbances which occur in the muscles of patients with progressive muscular dystrophy.

ROTHSCHILD, Foxborough, Mass.

INFLUENCE OF MOVING PICTURES IN AGGRAVATION OF NEUROSES. D. MARCONDES, Rev. Assoc. paulista de med. **3**:37 (July) 1933.

Marcondes' patient had anxiety hysteria, which was greatly improved by psychoanalysis, by which it had been discovered that she had unconscious desires of adultery and that she wished her husband's death. She suddenly became worse owing to the fact that she saw a moving picture the plot of which related to her inner conflict. The author compares his case with that reported by Wittels, whose patient fainted during a theatrical performance the plot of which was related to the unconscious roots of the patient's neurosis. Marcondes says that in cases of neurosis in order to obtain satisfactory results from psychotherapy by means of distractions it is necessary to have the patient avoid pictures the plots of which may cause psychic trauma. His case shows the value of psychoanalysis to psychiatrists in the guidance of neurotic patients as well as in the interpretation of the details in the evolution of neurosis.

EDITOR'S ABSTRACT.

CONDITIONS LEADING TO THE DEVELOPMENT OF PATHOLOGIC INTOXICATION. H. SEELERT, Monatschr. f. Psychiat. u. Neurol. **86**:191 (Aug.) 1933.

Seelert calls attention to certain resemblances between pathologic intoxication and hypoglycemic states. The occurrence of the latter following the use of insulin may lead to sudden outbursts of excitement which can scarcely be differentiated from pathologic intoxication. Hunger, bodily exertion and illness favor the development of pathologic intoxication as well as hypoglycemic states. Both conditions occur most frequently in young adults, and both may come on very acutely. In view of these common features, it is probable that the pathologic process operative in pathologic intoxication is the same as that which leads to hypoglycemia. There are centers in the interbrain which regulate the blood sugar level. The clinical picture of pathologic intoxication may be consistent with a disturbance of this regulating mechanism.

ROTHSCHILD, Foxborough, Mass.

CAN DIFFERENT WRITERS PRODUCE IDENTICAL HANDWRITINGS? ROBERT SAUDEK, Character & Personality **2**:231 (March) 1934.

The question is raised whether two different persons could, while writing quickly, produce a whole bulk of writing in a consistent style which would show all the idiosyncrasies of one personality and of no other. Samples of handwriting by four pairs of identical twins are pictured and discussed as representing writing produced by identical twins that would be considered identical by the criteria ordinarily used. Strikingly similar samples are presented of the handwriting of two unrelated girls, aged 11, from the same school for the deaf. About 5 per cent of 234 pairs of identical twins were found by Saudek to have identical handwriting. He believes that identical handwritings may be found once in specimens from about 10,000 persons.

MATHER, Howard, R. I.

SOMNAMBULISM IN CASES OF INTOXICATION. J. FERRAZ ALVIM and T. DE ALVARENGA, Rev. Assoc. paulista de med. **4**:20 (Jan.) 1934.

Ferraz Alvim and de Alvarenga study the rôle of nervous and toxic predispositions in the development of spontaneous somnambulism. They report a case of

hysterical somnambulism in a person with toxicomania and a typical case of toxic somnambulism in a patient with nervous miopragia. In the second case two rare facts were observed: (1) the motor activity of the patient during the attack, since he ran in somnambulation, and (2) the retaining of the imaginary causes which made him run during sleep and which he could narrate on awaking. The psychophysiologic mechanism of spontaneous somnambulism may be explained by a toxicosensorial stimulation during sleep which produces associated ideas, groups of images and visual and auditory hallucinations which compel the patient to perform the movements related to the dreams.

EDITOR'S ABSTRACT.

PSYCHOSES ASSOCIATED WITH PERNICIOUS ANEMIA: REPORT OF A CASE IN WHICH CURE WAS OBTAINED BY TREATMENT WITH AN INJECTABLE LIVER EXTRACT. ERIK GOLDKUHL, Acta psychiat. et neurol. **9**:29, 1934.

A man, aged 75, previously in good health, exhibited pernicious anemia with a secondary psychosis of the amentia type. After several liver preparations were tried without success, and while he was in a nearly moribund state, large doses of an injectable liver extract were administered twice daily, intravenously. In about ten weeks the patient completely recovered from both the anemia and the psychosis. No untoward effects were observed during treatment. In connection with this case the author reviews and discusses the literature on psychoses developing in the course of pernicious anemia.

YAKOVLEV, Palmer, Mass.

PROTEINS IN CEREBROSPINAL FLUID: METHODS FOR DETERMINATION; DIAGNOSTIC AND PROGNOSTIC VALUE IN CERTAIN DISEASES OF THE CENTRAL NERVOUS SYSTEM. O. LANGE, Rev. Assoc. paulista de med. **4**:153 (April) 1934.

Lange studied the nature, classification, division and pathologic significance of proteins in the cerebrospinal fluid as well as the methods for their detection and determination. He makes special reference to the methods used in the neurologic department of the Medical School of São Paulo. He reports the results that he obtained in cases of dementia paralytica with Kafka and Samson's method for the determination of proteins. The causes of the endogenous and exogenous origin of proteins in the cerebrospinal fluid in diseases of the central nervous system are considered.

EDITOR'S ABSTRACT.

CEREBELLAR ATROPHY: I. COSTA RODRIGUEZ and A. BORGES FORTES, Arq. brasil. de neuriat. e psiquiat. **15**:272 (Oct.-Dec.) 1932.

Costa Rodriguez and Borges Fortes report an anatomicopathologic study of a case of pontilo-olivary atrophy in which the olivary bodies, the lateral and reticular nuclei of the medulla oblongata and the fibers of the restiform body proved to be normal, while there was an intense degeneration of the middle cerebellar peduncle and less intense degeneration of the pontile nuclei. The anatomic observations of the authors conflict with those previously reported on the site of origin of pontilo-olivary atrophy, a condition which up to the present has been considered a primary abiotrophy originating in all cases in Essick's cellular bands, that is, in the inferior olivary nuclei, the nucleus arcuatus and the ventral nuclei of the pons.

EDITOR'S ABSTRACT.

CLINICAL FORMS OF LANDRY'S SYNDROME. A. DE CASTRO, Rev. Assoc. paulista de med. **2**:194 (April) 1933.

De Castro says that Landry's syndrome may appear as a primary polyneuritic form or as a complication of polyneuritis that is already established. In the first type the syndrome appears as an acute ascending motor polyneuritis. There may be an associated paralysis of the cranial nerves in this form. Acute myeloneuritis and neuronitis and febrile acute polyneuritis may be included. In the second type

the syndrome appears in the course of either toxic or infectious polyneuritis and follows a superacute evolution. Landry's syndrome in cases of alcoholic, arsenical, medicamentous and beriberic polyneuritis are examples of this form. A case of the latter type caused by malaria and another following vaccination against typhoid are reported.

EDITOR'S ABSTRACT.

INTRASPINAL DERMOIDS AND EPIDERMOIDS. SIDNEY W. GROSS, J. Nerv. & Ment. Dis. **80**:274 (Sept.) 1934.

The case reported is one of simple epidermoid tumor restricted to the second and third dorsal vertebrae on the left side of the spinal cord, which had caused recurrent attacks of bilateral sciatic pain with weakness and atrophy of the left lower extremity. After removal of the tumor there was improvement followed by a return of symptoms. A large tumor with its capsule was again removed at the site of the old lesion, which on histologic examination revealed no cells or blood vessels and no nuclei but only the inert lifeless appearance of the interior of pearly tumors which resemble the cross-section of a dead plant.

HART, Greenwich, Conn.

SLEEP AND MENTAL DISEASES. A. BOTELHO, Arch. brasil. de med. **23**:61 (Feb.) 1933.

Botelho reviews the anatomicoclinical work on which the knowledge of the localization of the centers of sleep in the hypothalamic region was based as well as the literature on the relations between the lesions of the subcortical nuclei and mental disturbances. He has studied the relation of sleep to hallucination, narcolepsy, somnambulism and cataplexis and the mechanism of the production of lethargy, stupor and cataleptic sleep. He emphasizes the pathogenic and diagnostic importance of disturbances of sleep in the interpretation of mental diseases.

EDITOR'S ABSTRACT.

PARAPLEGIC FORM OF EPIDEMIC ENCEPHALITIS. V. MAIERÁ JR., Rev. Assoc. paulista de med. **3**:61 (Aug.) 1933.

Maierá Jr. reports a case of the paraplegic form of epidemic encephalitis belonging to the third type of Gruchet and Verger's classification. The case simulated clinically a case of transverse myelitis. The author calls attention to the importance of examination of the cerebrospinal fluid, the clinical diagnosis in his case being based on the alterations found. The differential diagnosis is also discussed.

EDITOR'S ABSTRACT.

PARAPHRENIA, PARANOIA AND QUERULOUS PERSONS. J. DE MOURA, Arch. brasil. de med. **23**:72 (Feb.) 1933.

De Moura says that paranoia and paraphrenia (Kraepelin's) are well characterized mild types of schizophrenia which may be designated as schizophrenia of the paranoic and paraphrenic types, respectively. Querulous persons should be considered as corresponding to those with Bleuler's psychopathic reactions and not as schizophrenic paranoic subjects, since their ideas do not constitute a true form of delirium.

EDITOR'S ABSTRACT.

ASTEREOGNOSIS ORIGINATING FROM TRAUMA TO THE RIGHT PARIETAL LOBE: REPORT OF A CASE. BOURGAY DE MENDONÇA, Arq. brasil. de neuriat. e psiquiat. **16**:14 (Sept.-Oct.) 1933.

Bourgay de Mendonça reports a case of astereognosis originating from a traumatic lesion of the right parietal lobe. The condition in the case reported

appears to be of a permanent character. The lesion was caused during an assault. The case is studied from both the neurologic and the medicolegal angle.

EDITOR'S ABSTRACT.

SYNDROME OF THE OPTIC CHIASM: MELANOSARCOMA OF THE THIRD VENTRICLE EXTENDING TO THE HYPOPHYSIS. F. ROUSSEAU, Ann. d'ocul. **171**: 54 (Jan.) 1934.

A syndrome of the optic chiasm without hypophyseal manifestations was present in a youth, aged 19, with hemorrhagic diathesis. Necropsy showed a melanotic sarcoma of the floor of the third ventricle and extension to the tuber cinereum, the hypophysis, the optic thalami and the frontal lobe.

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GLIOSIS OF THE OCCIPITAL LOBES IN CASES OF CHOREA. DR. CHARLES DAVISON.

While most observers agree that the pathologic process in cases of chorea is situated mainly in the neostriatum, lesions have been found also in the dentate nuclei, brachium conjunctivum, cerebellum and cortex, alone or in combination with striatal lesions. It is not my purpose to describe in detail the histopathologic picture of chorea. This study will be limited chiefly to a gliotic process in the white matter of the occipital lobes. Except for Terplan's report (*Virchows Arch. f. Path. Anat.* **252**: 146, 1924) in one case of chorea (case 2) such observations have not hitherto been recorded. The material for this study was selected from 15 cases of chorea, in 8 of which the lesion was in the occipital lobe. For the material in 4 of these cases I am indebted to Professor Spielmeyer.

Five cases (1, 2, 3, 5 and 6) were of the type of Huntington's chorea. In case 4 no other member of the family was afflicted with the disease. The history of "grip" six months prior to the appearance of the involuntary movements suggested the possibility of encephalitis. Histopathologically, however, there was no evidence of an inflammatory process within the nervous system. The chronic chorea in case 7 was due to arteriosclerosis. Case 8 was one of hemichorea caused by thrombosis of a branch of the anterior cerebral artery, destroying part of the caudate nucleus and putamen and the upper third of the anterior limb of the internal capsule; the other cerebral vessels showed marked evidence of arteriosclerosis.

The pathologic process of interest is the gliosis in the white matter of the occipital lobe. Is this gliosis a primary process or is it secondary to destruction of the myelin sheaths? It is to be emphasized that small areas of demyelinization of the white matter of the occipital lobes with slight damage of single fibers were found in cases 6 and 7. Destruction of single fibers was seen also in the other cases (1, 2 and 4), but this was so insignificant that it was disregarded as a contributory factor to the dense gliosis. In none of the cases was there evidence of extensive fatty deposits in the white matter. A slight amount was found only in cases 1, 2, 3 and 6. Greater amounts of the fatty products occurred in cases 1, 5 and 6 in the gray matter of the occipital lobes, where there was involvement of the ganglion cells.

Extensive gliosis without appreciable destruction of myelin may occasionally be encountered in cases of anoxemia and encephalitis. The gliosis observed in cases of chronic inflammatory processes of the nervous system (encephalitis, dementia paralytica, etc.), of arteriosclerosis and of toxic degenerative disease (multiple sclerosis, amyotrophic lateral sclerosis, etc.) is preceded and accompanied by destruction of myelin sheaths. The fact that in some of these cases the white matter was not demyelinated and that fatty products were absent gives weight to the belief that the gliosis was primary. However, it is possible that the gliosis may have been secondary to slight destruction of myelin sheaths, since disintegration of myelin in the white matter of the occipital lobe, unless very extensive, cannot be demonstrated easily because of the abundance of the fibers and their complicated intercrossing. The possibility that the unknown agent causing Huntington's chorea acts on the white matter of the occipital lobes

and stimulates the growth of the glia fibers without the production of marked destruction of the myelin sheaths must also be considered. It is difficult, however, to explain the process in the two cases of arteriosclerosis (cases 7 and 8) on the same basis. In these the gliosis may have been due to anemia produced by the partial occlusion of a small vessel without destruction of the myelin. Whether the gliosis is a response to some chemical substance present in the perivascular anoxemic area or is a response to a deficient blood supply cannot be answered. Meningitis and neoplastic disease of the meninges probably produce gliosis of the brain tissue as a result of occlusion of the subarachnoid and perivascular spaces. To make sure that this type of gliosis does not occur in normal middle-aged or elderly persons, sections from the occipital lobes of normal persons were studied by the same method; in none was this type of gliosis noted.

The gliosis in the occipital lobes in these cases of chorea is of interest because so few cases are recorded in the literature. Terplan accidentally noted gliosis in 1 of 6 cases of chorea. In his instance, as in my cases, there was little destruction of the fibers of the white matter to account for the gliosis. Spielmeyer (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **101**:701, 1926) found similar changes in the occipital lobe in a case of Huntington's chorea which presented a clinical picture of Wilson's disease.

The gliosis may have some clinical significance. With such extensive involvement, some visual defects might be expected. An attempt was made to determine this in some living patients but, owing to the involuntary movements of the head, accurate plotting of the visual field could not be carried out.

DISCUSSION

Dr. Joseph H. Globus: From the pictures of the glia which have been shown in these sections nothing can be deduced as to what provoked the gliosis. It is unfortunate that material from other parts of the brain was not shown so that the glial content in other portions of the brain could be compared with the gliosis in the occipital lobe. Is it not possible that the glosis in the occipital lobe is an extension of a process elsewhere, and which is the etiologic background of the clinical picture?

Dr. Joshua A. Rosett: Were there manifestations of specific involvement of the occipital lobes, such as visual disturbances, hallucinations, etc.?

Dr. Charles Davison: The white matter of the convolutions from other parts of the brain did not show the intense gliosis observed in the white matter of the occipital lobes. The pathologic process noted in the 8 cases was that usual in chorea, i. e., essential involvement of the neostriatum and scattered lesions elsewhere. In my cases there was no mention of visual hallucinations, nor were the latter present in 2 living patients with chorea observed at the Montefiore Hospital.

Psychopathology of Time. Dr. Paul Schilder.

The perception of time has an objective and a subjective side, as do other perceptions. The immediate experience of time may be compared with sensation in other perceptions. The immediate time experience depends on libidinous factors. It is changed in states of déjà vu, depersonalization, obsession neurosis, depression and schizophrenia. In the process of depersonalization, narcissistic, voyeuristic and sadistic elements displace the immediate experience of the present into the past. "Present" means that one is able to enjoy oneself and to progress into the future. The patient with an obsession neurosis experiences time as an eternity of tortures. In depressions the passage of time ceases also since only eternity guarantees the continuation of destructive and self-torturing impulses. Schizophrenic patients lose the immediate living experiences of the ego in relation to time, together with loss of feeling to love objects. The patient with obsessive neurosis may treat time like a valuable object, equated with money.

In intoxication from hashish and mescal, passage of time may appear extremely slowed and space greatly extended. The alteration in experience of time is

closely related to changes in the direction of perceptions and variations in motility and tone. Similar phenomena can be observed in cases of alcoholic hallucinosis with vestibular symptoms and in vestibular and cerebellar lesions. In diffuse postinfectious disease of the brain time may be experienced as lengthened and shortened.

The exact appreciation of the length of time passed in sleep and hypnosis is based on the utilization of immediate time experiences by a constructive effort.

Past experience cannot be brought into correct temporal alinement in cases of the Korsakoff syndrome. A specific psychic function guarantees the reconstruction of the correct sequence of events in the past, but only when a constructive effort is made. The actual time experience is preserved in Korsakoff's syndrome, in which secondary elaboration is impaired. This dysfunction is partially dependent on lesions in the periventricular gray matter and especially in the cortex.

Psychic life contains an immediate foreshadowing of the future. Future is experienced as foreshortened, and words without definite content become hiding places for unanalyzed symbolic expectations. To understand the symbolic character of the life expectations of patients is a fundamental problem in psychotherapy.

The conception of a continuous flow of time extending from the eternal past into an eternal future is due to a process of complicated elaboration; it reveals as little of the psychologic facts as the physicist's approach to time. The conception of philosophers concerning time has failed to take account of immediate psychologic experiences and has substituted abstract thinking which does not cover the facts.

DISCUSSION

DR. CLARENCE P. OBERNDORF: Dr. Schilder has covered a vast range of time associations and time conditionings, offering interpretations on such widely divergent subjects as the psychopathology of time in neuroses and depressions, the alterations in time perception under drugs, the changes due to injury of the cells by alcohol in Korsakoff's psychosis, etc. I shall limit myself to the manifestations of time reactions as shown in clinical work with neurotic patients. I think that the first concept of time begins with feeding, that time perceptions begin in the interval between the time when the child has had its appetite satisfied and that when it again feels the need of food. This time appreciation soon becomes associated with the feelings arising in connection with regular evacuation of urine and feces.

It is probable that the concept of time antedates that of space. Indeed, certain psychoanalysts believe that the child does not appreciate space until he is several months of age and considers the mother's breast as part of his own body. The fact that the first impressions of time are probably intrasomatic does not exclude the idea of external movement in connection with time. The intrasomatic bodily movements continue to be as important as the movements of external forces which come later. As the child progresses he begins to rely on certain points of time fixation outside of body function, based on his own experience and on that of others; on these he develops his more mature concept of time. I think that all man's time experiences are in response to libidinous needs; the child fixes attention on certain physiologic libidinous experiences as epochs in time. These begin with feeding and later involve puberty, sexual relationship, menstruation ("regular as clock work"), marriage, parenthood and death.

The death idea apparently appears early in the time concept, and most neurotic patients who are pathologically preoccupied with the problem of time are also much preoccupied with the problem of death. Many of them have certain sadistic impulses which they feel they must perpetrate against others before death takes them. Interest in the death of others makes them worry about the problem of time in regard to themselves. Preoccupation with immediate time arises from concentration of the attention on body function. The problem of future time concerns itself with certain conceptions and dispositions taken from the outside world. The "time-worried" patient nearly always wishes in some way to have hostile or aggressive impulses gratified, and this brings the time problem in close

relationship to the so-called anal impulses. "Time is money," Dr. Schilder and others have said, and psychoanalysis has shown that interest in money is closely associated with fecal activities.

The schizophrenic patient withdraws from the immediate time experiences of the outer world with which he is no longer in harmony. There comes a regression from time perceptions of the outer world to those dependent on his own inner experiences.

The question of the symbolism of time is important. It is usually symbolized in masculine symbols, such as "Father Time" and "Old Man Sol." Death has nearly always a masculine symbolism. This leads to consideration of the problem of depersonalization, in which a conflict between certain masculine and feminine impulses seems to be the paramount issue, causing the patient to draw away from time through a feeling of unreality. Here, possibly, is a point of contact between preoccupation with time, which is the result of libidinal strivings, the conflict between masculine and feminine ideals and super-ego activities, which, as has been pointed out, are important factors in bringing about depersonalization and unreality, so closely connected with time problems.

DR. WALTER BROMBERG (by invitation): For some time I have been interested in the question of the development of the time sense. Time sense is a function that develops rather late in childhood. This arises from the general fact that time knowledge is an abstract concept involving subjective appreciation. From a broad point of view a child orients himself first through objective perception. The subjective world is an unknown, unnecessary, unreal world for the child. Piaget has said that the child has no understanding of any reality except an outer reality: "Everything is external and objective." Time is a difficult concept for children to acquire.

Numerous investigators have observed how difficult it is for a child to understand that "now" (today) can be yesterday or another day. "Children are concerned with things of the immediate present or the immediate future."

A study of the understanding of time among children shows that the main differences in the concept of time between them and adults are related to the power of abstract thinking. Even for adults the precise psychologic structure of the concept is not clearly understood. Nevertheless, every one has a rather definite innate sense of time. For adults time is a postulated frame of reference, an abstract but real factor in life; on it the whole of life's experiences seem to be arranged. For children it is at best a series of numbers and words related to positive objects which can be touched or seen and dealt with. From this object-meaning of time there develops a subjective meaning and a time sense.

The problem of memory for time in childhood depends in large part on the emotional needs of a past for children. There is no obvious connection or need for a past when there is a present. The egocentricity and the libidinous drives of children which demand immediate gratification influence their interest in, and development of, the time concept. Another factor in this development is dependence on the adult for the satisfaction of instinctual needs that depend on time intervals for their appearances, such as hunger, sphincteric activity, recurrence of day and night periods, etc.

The children studied in this paper covered a wide range of intelligence levels; some were of relatively low mental ages. In the examples given can be seen the progression from concrete references to more abstract ones. Thus, Bruce McD. (aged 4) said: "Time . . . it means the clock strikes." Clifford R. (aged 5 years) replied promptly to the question "What is time?" "10 o'clock." Ida V. (aged 6 years) said: "Time is to get up out of bed; you wash your hands."

A beginning development along lines of the adult notions is seen in the responses of Arthur U. (aged 9 years): "Time is 11 o'clock, or 8, or 9." And even more in those of George H. (a Negro boy, aged 10 years, with mentality bordering on deficiency): "Time is how many hours does the hand go around the clock." Joan B. (a superior child, aged 5 years) said: "Time is the minutes that go; in the morning they come, in the night they go. . . . The minutes come from the clock." She thus related the idea to cosmic occurrences.

If one asks about age, however, one finds that children have an appreciation of old age and of youth, but less clearly of infancy. They have a clear idea of what is meant by young and old. Since children think in objective terms, it was thought advisable to question them in more concrete terms. From the examples quoted here it can be seen how much more accurate is the idea of time in relation to body conditions. Thus, Rita H. (aged 3 years, of average intelligence) said in reply to the question "How old is an old man?": "4 years." "How old is doctor?" "Young, 4 years." Charles G. (a boy, aged 8, with mentality bordering on deficiency) said: "An old man is 21 years. An old woman is 15 years. I am 8 years old. I'm young.' Dolores R. said: "An old man is 6," but she added: "An old man has a wrinkled face and gray hair." In the foregoing examples the child gave an excellent description of the essential features of age. He picked out the signs of involution unerringly—the loss of motility, the loss of ability to eat large quantities, decrease in height and weight, loss of tissue, etc. The difference between a child and an old person, or a young person and an old person, was attributed to the physiologic changes in skin, hair, bones and tissues. For example, Arthur U. said: "When you don't eat, you are old." Bruce McD. said: "An old person has cracks in his face; then they take him to a hospital, he dies, they put nails in them. . . . They cut one foot off a man and then he walks with a cane. An old man is skinny; he doesn't eat much; he doesn't grow and he dies."

The aggression of the child against his parents and other old persons in his environment appears in the ease with which a child conceives of old people as dead. Michael M. said: "When you get old you eat and bust up and die." The general notion that eating makes for growth, and decrease in eating makes for involution is significant of the oral sadism of childhood. The satisfaction of oral libido and the gratification of narcissism in motility are pleasures which the child cruelly denies to older persons. Feelings of guilt against aggression toward parents supervene early, modifying judgments, especially of parents. Thus, Theresa H. said after relating the pleasures of childhood play: "But old people can go to parties." Religious training provides a further illustration of this modifying influence. Thus, for children, the age of God is quantitatively great, but He does not have the objective qualities of old age—weakness, lack of motility, etc. Children all agree that God is an old man, but He is universally described as a vigorous man. Even as an old man, God takes on many of the characteristics of a punishing father. Thus, Edwin San L. (aged 6 years) said: "God is an old man; He could take you in the sky when you say bad words. He is 7 years old." Another child said: God may have "white whiskers like Santa Claus" but can "take you in the sky" if you disobey Him or your parents. Also H. (aged 10) said that "God is an old man, but an old man is older than God" (i. e., more infirm).

One sees, then, how complex are the influences that go into the development of abstract notions in children. Emotional factors, gnostic functions, subject-object relationships and environmental influences are all involved in the development of the idea of time.

Dr. Smith Ely Jelliffe: Dr. Schilder's paper has stimulated a number of thoughts. The subject is full of suggestions for medicine. When I say I promise not to "consume too much time" it may be noted that I am not far from the old myth of Uranus and Chronos, the possible interpretation of which Dr. Schilder has mentioned. This "consuming of time" as related to pathologic conditions of the gastro-intestinal tract is of much clinical significance. The greedy—so-called "hungry" person—develops a host of dyspepsias, spasticities in the upper part of the gastro-intestinal tract, from his sadistic attack on time. He cannot swallow fast enough; the stomach demands gratification faster, and many symptoms develop which need psychotherapy more than diet or bromides. Similarly, at the other end of the intestinal tract consider those who would also "kill time" on the toilet—by constipation and by equally faulty handling of anal erotic impulses in the time frame of reference. In fact, the time element, as Dr. Schilder said, as well as that of space, enters into practically every activity of life, and unless they can

analyze or obtain an understanding of the kinetic, i. e., the motility, relationships, in order to do what they wish to do in terms of time, physicians will never understand what is happening in the human body.

Regard for a moment certain instances of kinetic situations in the sphere of speech, viz., stuttering. Think of the sadistic attitude of the average stutterer and the way he "wastes" (destroys) the other fellow's time, and how the listener anxiously tries to "grasp" the time element while the stutterer is sadistically keeping him away. The stutterer thus presents a classic type of "time destroying," which in less pathologic forms is seen in persons who are always late for appointments.

In the muscular sphere, I have been much interested in the study of myotonia congenita. The patient starts to do something, is held up and cannot do it. He closes his fist, and he cannot open it; he jumps and cannot go on. A patient of mine is afraid to jump into the water to swim because he may drown before he can get the activities of his muscles into their proper time relationship. Here, in my opinion, is another illustration of the sadistic relationship of the musculature in the attack on time. A similar fantasy relationship I have found in certain cases of myasthenia gravis, although this is not so capable of proof.

Dr. Schilder says that he is not much interested in the philosophic attitude; neither am I, and yet I cannot refrain from quoting the philosopher, Bergson, who in his "Time and Memory," wrote: "The future, which we dispose of to our liking, is filled with an infinity of possibilities. Even if we get the most coveted of these, we must give up all the rest. That is what makes fantasy so much pleasanter than reality." Think of all the things that must be given up when one lives in reality, as compared with what one would like in fantasy. Dr. Schilder has given numerous illustrations of fantasy types of thinking in Korsakoff's psychosis, drug intoxication, etc. Is it any wonder there is an alcoholic problem?

I shall speak only briefly of the time sense as related to the cardiac activity of the mother and the fetus in the body. At a meeting of the American Neurological Association in Boston, when Stewart Paton was speaking of fetal cardiac activities, I ventured the suggestion that possibly Irving Berlin's jazz compositions had something to do with the irregularity of his mother's heart beat which he heard as a fetus. Incidentally I was able to say that I had previously made that remark in a medical society meeting, and a physician in the back row arose and said that she had a cardiac irregularity. Its time quality was of the nature of some of her son's most outstanding jazz productions.

DR. GEORGE H. HYSLOP: One can properly define the sense of time as the awareness of the sequence of events. If my memory is correct, William James, as long ago as 1890, made such a definition. The experiments of Wundt and his writings lead to the same definition. James also generalized to the effect that the development of the time sense proceeded pari passu with intellectual development and appreciation of events occurring within and without the body.

Another feature that is interesting to speculate about philosophically is why as one grows older he has the idea that time passes much more quickly than it did in earlier years. James discussed this point in simple terms.

DR. ISRAEL S. WECHSLER: The paper of Dr. Schilder deserves thoughtful consideration. It seems to me that too much emphasis was put on the relationship of the libido to time in organic neurologic disease. That emotion affects the conception of time is well known; if one spends an hour with a lovely woman it seems like a minute, whereas if one spends the same time with a bore it feels like days. Obviously pleasure shortens the sensation of time and pain increases it. I shall not discuss the philosophic conception of time, the question of sequences or its connections with movement, position and space. Neurologically, there is no evidence that the cerebellum or vestibular apparatus has anything to do with conceptual thought. Though lesions of the frontal lobe are characterized by mental and physical akinesia, that is, impaired movement, one finds no disturbances in time concepts. Such disturbances, however, do occur in lesions of the temporal lobe. Déjà vu phenomena are common in cases of lesions of the temporal lobe.

A patient of mine who had such a phenomenon was analyzed for twenty-two months. He had momentary spells consisting of a peculiar sexual sensation in the pit of the stomach, which lasted a fraction of a second, then of a déjà vu phenomenon, which was as brief, and finally a feeling that he swallowed his Adam's apple. The condition was interpreted as a compulsive neurotic phenomenon with peregrination of the libido. My diagnosis was glioma of the temporal lobe, which was verified by encephalography and operation, and unfortunately also by necropsy. The concept of time, as related to the cerebral cortex and embracing both visual and spacial perception, has to do with the temporal and occipital regions. Perceptions of space and depth are associated with the outer surface of the occipitotemporal lobes. I once saw a carpenter who had a minute cerebral hemorrhage into the occipital lobe and who lost the conception of depth and of spatial orientation. Hitherto he had been able to gage very small distances with his naked eye; subsequently he lost that ability. The element of vision, then, seems to me more important than any other in its relation to time. Though alcohol affects the cerebellum, acute alcoholic ataxia being cerebellar in nature, alcohol also decorticates. In intoxication from hashish, too, the outstanding disturbances are in the sphere of visual and spatial orientation, and therefore in time relationship. If, therefore, one wishes to speak of the pathology of time and its relationship to the anatomy and physiology of the brain, one can better correlate the concepts with lesions of the temporal and occipital lobes because they have to do with visual and spatial orientation and therefore must underlie the normal conception of time.

DR. JOSHUA ROSETT: A few years ago I reported the action of an instrument which has the effect of inducing sleep (ARCH. NEUROL. & PSYCHIAT. **22**:737 [Oct.] 1929). One of the features of induced sleep is that, unlike ordinary sleep, the person loses almost entirely the sense of time. Three years ago I made a large number of experiments with this apparatus (ARCH. NEUROL. & PSYCHIAT. **26**:131 [July] 1931). The subjects slept, and all lost the sense of time to the extent that when asked: "How long have you been asleep?" the uniform reply was, "A few minutes," when as a fact the sleep lasted one or even two hours. From a study of this induced sleep I concluded that the effect produced by the apparatus in question was that of general neural inhibition. The person is subjected to the action of a single stimulus, i. e., a wave of gentle compression of the limbs and body which travels from the extremities to the upper part of the chest, and all other stimuli are excluded as far as possible. The effect is therefore paralleled by Pavlov's experiments in which a dog falls asleep under the influence of a single stimulus.

Since this apparatus may be said to induce a general neural inhibition, it provides, I think, an explanation for the subject's loss of time sense. Time is a succession of events, and one is aware of the succession of events through the senses. Any disturbance of the senses, therefore, must result in an incorrect perception of time. It makes no difference whether it is a tumor of the brain, or a state of embarrassment or of pain, in which time appears to be lengthened, or a state of pleasure, in which time appears to be shortened.

In consideration of these facts it is difficult to see why the speaker wishes to make the conception of time dependent on libidinous strivings as modified by vestibular impulses.

DR. PAUL SCHILDER: I can be brief concerning the libidinous factors in time perception since Dr. Wechsler has already pointed out how quickly time passes when one is in a state of agreeable libidinous tension. It has been said that the time factor is determined merely by perceptions. But is one not a human being when one perceives? Does one not have definite interests in connection with every perception? This personal libidinous factor is paramount in appreciation of the time past. Dr. Rosett made the interesting remark that one does not appreciate time correctly when one sleeps. I cite a pertinent experiment showing that one does have an accurate perception of time when asleep.

DR. JOSHUA ROSETT: I spoke about this particular form of sleep.

DR. PAUL SCHILDER: Dr. Rosett's remarks are of interest in the following way: There is not one system of experiences; there are several. I was interested to learn how amnesic patients perceive the passage of time. Some patients with amnesic gaps for several months regarded the last event before the gap as if it had been yesterday. Other patients measured the time elapsed during the amnesic gap correctly, and others believed it lengthened. When one fills up the amnesic gap by hypnosis or by other psychotherapeutic measures, the patient regains an exact appreciation of the lost time. There is a superficial time experience, which may be incorrect. In order to reach a true appreciation of the time that has passed one must use a constructive effort, and then one appraises time accurately. Even Dr. Rosett's subjects would appreciate time correctly if they were forced to construct accurately.

Every experience of the senses contains an element of motion. Objects are never at rest. The greater the primitive sensual experience, the more is motion in the foreground. Motion and movement are always in time. Time is always present and therefore cannot be derived from any other experience. Like any other sense impression, the primitive time experience must be worked out by continued effort.

Dr. Oberndorf has given an excellent explanation of time disturbances from a psychoanalytic point of view, but I beg to differ from the general psychoanalytic conception. I do not think that the knowledge of body precedes knowledge about the world. If one does not know enough about the world one does not know anything about the body. A constructive effort must be made in order to gather a sufficient knowledge of the body image. I agree with Dr. Wechsler that time experience is connected with every experience concerning the outside world. Difficulties in the perception of time may arise also from difficulties in perception due to cortical lesions. I did not discuss these details. I do think that the déjà vu phenomenon is generally a libidinous phenomenon. Fortunately, many who have experienced déjà vu phenomena do not have gliomas of the brain.

I wish to emphasize that the study of time perception gives a general insight into what I would like to call the constructive forces of the psyche.

PICK'S DISEASE: CLINICAL AND PATHOLOGIC CONSIDERATIONS. DR. ARMANDO FERRARO and (by invitation) DR. GEORGE A. JERVIS.

Pick's disease developed in a man aged 50 after an attack of influenza. The patient became more and more indifferent, apathetic and disinterested, and seldom talked spontaneously. When admitted to the hospital he was quiet, indifferent, taciturn and inactive. There was a real affective emptiness. The memory was good for remote events but poor for recent ones. At times he did not answer, justifying himself by saying: "I cannot think now." Tests of thinking capacity, attention and mental tension confirmed the inability to concentrate; insight was lacking. Orientation was fair. No hallucinations were elicited. The pronounced lack of concentration became more and more evident, and the patient lost contact with his surroundings, while impairment of all intellectual activity progressed gradually. Diminution of spoken language, which was reduced to a few words and short sentences repeated over and over, was reported. In March 1933, ten years after the onset of the first clinical signs, the patient died in a state of complete dementia.

We believe that the clinical picture fits the standard outline of Pick's disease which in early stages is characterized by hindrance to expression of the intellectual functions, a sort of interference with the activation of the mental mechanisms and consequently inertia of the processes of thought. There were, in addition, the typical fluctuation of the level of attention, distractibility and the preservation of memory in terms of conservation of mnemonic engrams. Aphasic manifestations, not to be confused with the limitation of language due to reluctance to talk, completed the clinical picture characteristic of Pick's disease.

Pathologically, the brain showed circumscribed cortical atrophy of the frontal and temporal lobes on both sides, with predominance of the lesion on the right side.

Histologically, all features of Pick's disease were present. Atrophy of the nerve cells was associated with characteristic swellings and argentophilic cellular inclusions. Senile plaques and Alzheimer's neurofibril alterations were absent. Moreover, the examination brought out the absence of elements supporting the conception of a heredodegenerative condition. We were unable to find a predilection of the atrophy for the neocortex, for certain cortical cyto-architectural areas or for any particular layer of the cortex.

We have failed also to confirm the analogy between the cellular changes in this case and those in cases of Tay-Sachs' disease. Inclusions and acute swellings, as present in this case, are not pathognomonic of Pick's disease. The extracortical lesions may be explained on the basis of secondary involvement resulting from atrophy of the cortex.

The cellular lesions were irregularly distributed in all layers of the cortex—at times in the external and at others in the internal layers; many lesions are comparable with those described in arteriosclerosis by Spielmeyer (*Monatschr. f. Psychiat. u. Neurol.* **68**:605, 1928) and his co-worker (Neuberger in Bumke: Handbuch des Geisterkrankheiten, vol. 2, p. 520). Here and there the areas of atrophy involved the territory of distribution of small blood vessels.

Though upholding the findings of the majority of authors that no arteriosclerotic changes of the blood vessels are encountered, we believe that a considerable amount of the atrophic process is due to a functional vascular condition, more precisely to a vasospasm. What produces the angiospasm is still unsolved? Does the angiospasm involve predisposed tissue, a tissue in which a toxic process is active or a tissue precociously old, so to speak?

From the standpoint of the interpretation of the clinical symptoms, we think that with the exception of the aphasic symptoms most of the clinical manifestations in this case can be attributed to severe involvement of the frontal lobe, as such clinical manifestations fit into the picture described in numerous cases of neoplastic or traumatic lesions of the frontal lobe.

DISCUSSION

DR. CLARENCE O. CHENEY: Clinically, the history in this case is one of a slowly progressive but deep organic deterioration. It would be difficult to distinguish it from the deterioration in Alzheimer's disease; at the time of the patient's death that distinction had not been made. There was no evidence clinically of an arteriosclerotic process or of cardiovascular disease. The systolic blood pressure was not more than 110.

Although the gross appearance of the brain suggests a similarity to Alzheimer's disease, the atrophy is more localized and focal in certain areas than it is in Alzheimer's disease, and the microscopic picture is different. Senile plaques are absent; there is some neurofibrillar alteration, but in no place are there the basket cells of Alzheimer's disease. As Dr. Ferraro has indicated, the distribution and nature of the lesions suggest the type frequent in vascular disease, but there is no distinct or outstanding vascular disease with which one can correlate the lesions. The microscopic picture suggests to me a more or less slow death of tissue, which could have been produced by various mechanisms. It might have been caused, in a complete and extensive way, by completely cutting off the blood supply by thrombosis, but it does not seem that this has occurred in this instance. Again, it might be caused by diminution in the blood supply, only half of the necessary nutrition reaching the tissues; this would undoubtedly have an effect on cerebral structure and function. The blood supply depends not only on the size of the vessels but on the strength of the heart. There was no distinct clinical evidence of cardiac disease, but autopsy showed a rather large heart in diastole, and there was certain evidence of coronary occlusion or thrombosis. It occurs to me that the blood supply to the brain may have been interfered with by lack of cardiac force in spite of the fact that the vessels in the brain and elsewhere in the body did not show atheromatous changes. Nutrition may also be interfered with by failure to remove waste products from the areas in which they accumulate. However, there was no accumulation of fat or lipoid material.

One should consider also the possibility that there is some biochemical change in the tissue itself, perhaps an original short life span of the tissue. That there is a toxic or noxious factor to be considered is indicated, I believe, by evidence of axonal degeneration—changes similar to those in pellagra and in acute and sometimes in chronic alcoholism. In the latter the disturbance may be due not directly to the toxin of alcohol but to an indirect metabolic disturbance caused by the alcohol, perhaps of the liver, with disturbance in its function and secondary indirect effects on the function and structure of the brain. I have seen axonal alteration in cases of alcoholism in which the patient had not had alcohol for a number of years, and I think that the disturbance brought about by the use of alcohol may be continued over a period of years. A similar mechanism of disturbed function may perhaps be operative in cases of Pick's disease.

Dr. Ferraro suggested vasospasm. He may be correct, but it is difficult to demonstrate or to prove the influence of this factor. Perhaps there are changes in the colloidal reactions; there may be a dispersion of colloids which is associated with death of tissue. It is not a reaction similar to that seen in cases of amaurotic family idiocy. I think that an understanding of this type of lesion will come through a study of biochemistry in the living person. All possible physiologic tests should be carried out in cases of certain organic changes in the brain to determine what is going on in the living body, so that when the patients die one may see what is the relationship between the physiologic changes that occur during life and the evidence of altered metabolism in the brain observed at autopsy.

DR. LLOYD J. THOMPSON (by invitation): I have seen six cases of Pick's disease, but in only one did I have an opportunity to make clinical observations over a period of three years. In 1892, Arnold Pick, being interested in aphasia, selected some senile brains for study and sought for focal lesions. A little later he recognized that there was something different in the brains selected from the ordinary senile brain; but it was not until the turn of the century that investigators began to define this condition as a special clinicopathologic entity and classified it as presenile psychosis. Clinical findings and anatomic changes continued to be reported in Germany, but there were practically no references in English until some articles appeared in England in 1931 and 1932 (Critchley: *Lancet* **1**:1119, 1931; Thorpe: *J. Ment. Sc.* **78**:305, 1932); it was 1932 before anything definite on Pick's disease was published in the American literature (Hoedemaker and Mathews: ARCH. NEUROL. & PSYCHIAT. **28**:1149 [Nov.] 1932).

The causation of Pick's disease is still unsettled. Reports have come from Germany describing Pick's disease in two brothers (Grüntthal: *Ztschr. f. d. ges. Neurol. u. Psychiat.* **101**:128, 1926) and again in three sisters (Schmitz and Meyer: *Arch. f. Psychiat.* **99**:747, 1933; Braunmühl, *Zentralbl. f. d. ges. Neurol. u. Psychiat.* **69**:232, 1933). There are descriptions of the condition occurring in two generations in the reports of Schmitz and Meyer and Braunmühl and of Grünthal (*Ztschr. f. d. ges. Neurol. u. Psychiat.* **136**:464, 1931); a questionable case of Pick's disease was reported in the third generation by Schmitz and Meyer and by Braunmühl. However, the presence of the disease in grandparents must be speculative. These cases are on record, however, and when it is remembered that only 100 cases have been reported, not much can be said with certainty about the hereditary factor.

In regard to vascular disturbances as a possible etiologic factor, high blood pressure and arteriosclerosis are peculiarly absent in Pick's disease. Extreme variations of blood pressure and the usual evidences of vasomotor disturbances have not been noted. Krapf (*Arch. f. Psychiat.* **93**:409, 1931) has stated that epileptiform seizures are seen in cases of Pick's disease only in the presence of hypertension, and such cases are rare. Nevertheless, I suppose that it is possible that some cerebral vasomotor disturbances which are not well understood may be a primary or perhaps secondary factor.

I do not believe that alcoholism has been reported in many cases, and as far as I know from the literature dietary deficiency has not been apparent. Certainly in my cases I am sure that it was not a factor, that is, so far as one can judge from the ordinary history about diet.

Another point I wish to make concerns the possibility of diagnosing Pick's disease prior to autopsy. Dr. Kahn and I believe that frequently the diagnosis can be made ante mortem, based not on any one or two characteristic symptoms but on a general survey of the whole history of the development of the disease and on the shades of differentiation in the various presenting symptoms. Differentiation between Pick's disease and Alzheimer's disease presents the greatest difficulty. In Alzheimer's disease memory per se is usually affected definitely in the early stages, whereas in Pick's disease the patient does not have access to memory as a sort of intellectual tool, but varying amounts of memory persist for a long time. We have been able to demonstrate this by special psychologic tests. In regard to memory, then, there are shades of differences which help considerably in establishing a diagnosis. Encephalograms also will help. In Pick's disease there are large confluent collections of air over the frontal and temporal regions, but in Alzheimer's disease the air appears distributed in streaks or bands, as a rule. Flügel (*Ergebn. d. inn. Med. u. Kinderh.* **44**:327, 1932) published some interesting encephalograms illustrating these points.

A few other factors for use in differentiation may be mentioned. Alzheimer's disease has been known to start at an earlier age than Pick's disease. In many cases of Pick's disease there is a definite stage of hyperactivity, followed by a stage of hypo-activity; the latter is probably the stage of the disease presented by Dr. Ferraro's patient when he entered the hospital. These two stages stand out in Pick's disease in contrast to Alzheimer's disease. The general course in Pick's disease is: first the change of personality, then the hyperactive stage, followed by the stage of hebetude, and finally complete dementia. I may mention that epileptiform seizures and focal symptoms, which occur in Alzheimer's disease rarely appear in Pick's disease. Spontaneous speech, logoklony and confabulation are all more characteristic of Alzheimer's disease.

With further detailed studies of the total clinical pictures one should gradually increase the percentage of diagnoses made before death of the patient.

Dr. Ferraro's demonstration of his pathologic material shows without doubt that the case was one of Pick's disease.

Dr. Armando Ferraro: I agree with the remarks of Drs. Cheney and Thompson. In the early stages of the disease it is possible to make a diagnosis during life, particularly if the characteristic changes in memory and the fact that hallucinations, delusions and confabulations are more common in Alzheimer's disease are given consideration. It is also important to remember that iteration and, particularly, logoklony are more frequent in Alzheimer's disease. Moreover, the encephalogram may be of help in diagnosis.

I agree that a toxic condition resulting from a metabolic imbalance might be the basis of the disease; it is possible that such a causal factor might interfere with vasomotor regulation and establish the imbalance of the vasomotor system responsible for most of the pathologic changes.

By referring to the vasomotor changes analogous to those described in arteriosclerosis by Spielmeyer and his co-worker, I wish to make clear that the vasomotor spasms do not necessarily require the existence of arteriosclerotic changes of the blood vessels and that mention was made of arteriosclerosis only to point out a condition in which vasomotor changes are more frequently encountered.

Reactive Psychosis in Response to Mental Disease in the Family. Dr. Loretta Bender (by invitation).

Those who care for the mentally sick and must deal with relatives of the patients are continually impressed with the marked emotional responses of the relatives. They show anxiety, agitation, indecision, distrust and feelings of guilt. The incidence of mental sickness in the family will arouse concern not so much about the complexes of the patient as about the complexes of the relative with whom one is talking. In the following cases at the Bellevue Psychiatric Hospital,

the pathologic emotional state in a relative reached a magnitude sufficient to characterize it as a psychosis.

In case 1, a sister reacted to schizophrenia in her brother which necessitated his commitment. She had an episode of anxiety depression, with preoccupation about her own sex problems, feelings of guilt in relation to her brother's sickness and a tendency to suicidal thoughts. She thought that she was losing her mind as her brother had. She recovered under treatment. Two years later, when the brother died in a state hospital, she had a recurrence of the same symptoms, returned to the hospital and again recovered. An important fact was that the father had been dead and that these, the two oldest siblings, had supported the family for years. The brother's emotional relationship to the sister was therefore not only that of a brother but also that of a father and that of a partial heterosexual love object, as she had made no other attachments. Several similar sister-brother relationships have been observed.

The next case is one of a sister reacting to mental illness in a sister. They were two younger sisters in a large family; the other siblings had made good adjustments in their own homes. The youngest sister was married but was still deeply attached to her father and lived near him. The second youngest had been ill with schizophrenia for many years but was cared for by the parents in their home. She had been brought to the hospital for observation, but the father removed her, being unable to decide on commitment. Shortly after this the father died after a prolonged sickness in which the younger sister nursed him. She was despondent over his death but took her mentally sick sister to live with her as a labor of love left to her by her father, against the wishes of her husband. As the mental symptoms of the sister made her home care difficult, the younger sister brought her to the observation hospital twice before she could overcome her indecision to commit her. Shortly after commitment the patient died in a state hospital. This precipitated a depressive anxiety state in the younger sister, which necessitated hospital care. She presented many obsessional trends, with preoccupations at first of feelings of guilt about her sister, which gradually gave place to concern about herself. She always claimed that there was nothing the matter with her and that the physicians thought she was ill only because her sister had been. She claimed that an effort was being made to cause her to follow the same destiny as her sister. Three months after commitment she recovered, with good insight and with a much closer attachment to her husband.

In another instance of sister-sister relationship the oldest sister in a large family had stepped into the father's position when he died, had supported the family and had dominated the family life. She lived out her romantic life vicariously through a younger, more frivolous sister, who had been married twice but was without children, which she wanted. The younger sister finally became pregnant, but when serious complications at the time of delivery frightened her admitted that she had become pregnant by an illicit lover. After delivery the patient passed into a postpartum depression. The older sister also became depressed and said that she had the same symptoms as the young mother. When the patient was sent to a hospital, the older sister began to have relations with the illicit lover of the younger sister because he said that she reminded him of the younger sister. She later blamed herself for this and became depressed, anxious and agitated, so that she needed hospital care about nine months after the younger sister. In the hospital she discussed her problems; after the younger sister recovered from the depression and visited the older sister, she too recovered and returned home and to work.

Several cases of mothers who reacted to the mental illness of daughters have been observed. Important features in these cases are that the fathers of the daughters had died previously and the mothers tended to identify themselves with fantasies concerning the love life of the daughters. There was a great deal of preoccupation and self-accusation on the subject of venereal infections.

Mothers who reacted to mental illnesses in their sons were also women whose first husbands had died. The sons seemed to represent the lost first love. These

mothers showed a tendency to try to cure their mentally sick sons with some form of magic or religious ritual. In one case the mother went to the hospital with the patient and for a period of more than a year, in which the catatonic state of the son had shown no improvement, was content to sit and wait in an apparently benign mental state.

These are not cases of folie à deux since the psychosis of the reactive relative is not the same as the psychosis of the beloved one. There are no identification processes in accepting delusional ideas. The reaction is an emotional disturbance, and the reacting relative usually has an objective attitude toward the psychosis of the beloved one. The attitude is one of self-accusation, emotional identification and preoccupation with one's own emotional problems. These are reactive psychoses in the sense that there is a constitutional weakness suggested by the family history of mental illness and sometimes also by previous episodes in the reactive relative as well. There are also precipitating factors of emotional quality. The important feature in the mechanism is that the beloved relative represented a double or triple relationship, usually owing to a previous death of another relative. Thus, a beloved brother may have represented, as well, the dead father and the heterosexual love object for sisters who had not yet made a heterosexual adjustment; or a son might represent the dead first husband to a mother. The psychosis was usually of an anxiety depression type. It might show schizophrenic features when the family history showed schizophrenia or features imitative of the mental illness of the first relative when the identification processes were very strong; or it might show compulsive and obsessional features when the reacting relative was a poorly integrated personality with neurotic fixations. The prognosis of the reactive psychosis was generally independent of the prognosis of the mental illness in the first relative. In general, the prognosis is good but dependent partly on the destiny of the beloved mentally sick relative and partly on psychotherapy directed toward the psychic mechanisms involved.

DISCUSSION

DR. CLARENCE O. CHENEY: The question arose in my mind whether it was in conformity with the usual terminology to call the condition in these cases a reactive psychosis. My conception of a reactive psychosis, for example, is that the depression is a reaction to a specific obvious external cause and that the content of the psychosis concerns itself with the cause; that is, when a depression results following the death of a relative, the person who is depressed is concerned fundamentally with the death of the relative. It seemed to me from Dr. Bender's description that these might better be called precipitated psychoses; they have been precipitated by the psychosis in relatives. Although to a certain extent the content of thought of the second person shows a relationship to that of the first that does not by any means always hold. The second patient not infrequently, as I gather from the presentation, is concerned more about himself and more about his own difficulties than about the first patient. As a fact, as Dr. Bender has indicated in one case of dementia praecox, the girl who was supposed to have had a reactive psychosis had previously had a psychosis before her brother showed any signs of trouble, which indicates that the brother's psychosis was merely another precipitating cause of the psychotic reaction on her part. In another case a sister had a distinct psychosis after the brother came home and said he was insane, but the history indicates that she had given up work and had been "hysterical" previously. There are various factors in these precipitations. One might conclude that in some of the families almost any cause might have been a precipitating factor.

Dr. Bender did not present the combination of the father-daughter psychosis, that is, a daughter having a psychosis following a psychosis in the father. Hers were all sister-brother, sister-sister, mother-son or mother-daughter relationships. I may say, however, that I have seen psychoses in daughters following the development of mental illness in the fathers.

The paper calls attention to a factor which is sometimes neglected, and that is the significance of the illness of a patient to relatives. There is nothing more demoralizing in some families than a case of mental illness; because of that relatives should be treated as kindly as the patients, with consideration and explanations, particularly when the question of commitment or transfer to a state hospital arises.

DR. CLARENCE P. OBERNDORF: In all of Dr. Bender's cases there has apparently been a strong identification of the original person with the person who subsequently became ill. While Dr. Bender has pointed out that these are not cases of folie à deux in the sense that they are complementary psychoses, nevertheless the factor of identification has been important. It seems to me, in the first case, that there may have been an identification of the brother with the sister when she had her first illness, before he was shot and before he became schizophrenic. The recurrence of identification in all the cases raises the question as to what degree of inversion of the sexual strivings existed in each. In the so-called folie à deux it is apparent that the only reason that folie can occur is that the libidinous strivings of the one person are complemented by the libidinous strivings of the other. The first case of Dr. Bender seemed particularly corroborative of this. These conditions might be termed identification psychoses rather than precipitated psychoses.

DR. LAURETTA BENDER: I wish to express my thanks to Dr. Cheney for suggesting the name precipitated psychosis and to Dr. Oberndorf for the name identification psychosis.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Feb. 21, 1935

C. A. MCDONALD, M.D., *Presiding*

SUBDURAL HEMORRHAGE: ITS OCCURRENCE AMONG PSYCHOTIC PATIENTS; A STUDY OF 245 CASES OBSERVED IN 3,100 CONSECUTIVE AUTOPSIES. DR. ANNA M. ALLEN, DR. BLANCHE B. DALY and DR. MERRILL MOORE.

In the twenty years between 1914 and 1934, 3,100 patients who died suddenly or unexpectedly in hospitals for mental disease in Massachusetts have been subjected to autopsy by the state pathologist. At these autopsies 245 cases of subdural hemorrhage (7.9 per cent) were found. One hundred and forty-eight of the cases occurred in males and 97 in females. The great majority of the patients were between 40 and 70 years of age, and a relative increase in the incidence of subdural hemorrhage was noted with advancing years.

When grouped according to psychiatric diagnosis, the greatest number of subdural hemorrhages were found in patients with psychoses associated with organic diseases of the brain in the following order: (1) epilepsy (124 subdural hemorrhages per thousand autopsies), (2) dementia paralytica (104 per thousand autopsies), (3) psychosis with cerebral arteriosclerosis (103 per thousand autopsies), (4) senile psychoses (87 per thousand autopsies) and (5) alcoholic psychosis (83 per thousand autopsies). Table 2 contains most of the data indicating the most frequent types of psychosis in which subdural hemorrhage occurs.

In 35 of the 245 cases in which subdural hemorrhage was noted at autopsy, that lesion was considered as the primary cause of death. The subdural hemorrhages were seen in equal numbers on the right (64) and left (58) sides in the 122 cases of unilateral lesions, and bilateral bleeding was found in 87 cases. The convexity was solely involved in 207 cases.

Subdural hemorrhages were found in the falx, in the tentorium and in the cerebellum each in 1 case. Variations from small circumscribed lesions to hemorrhages extending over an entire lobe or even over the entire hemisphere were noted.

TABLE 1.—*Age at Death (in Groups of Decades) in Cases of Subdural Hemorrhage*

	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	Unknown	Total
Males:												
Autopsy performed in all cases	27	43	98	220	313	334	341	201	71	4	16	1,688
Subdural hemorrhages	1	3	3	14	27	33	30	18	17	0	0	148
Incidence of subdural hemorrhage, percentage	3.7	7.0	3.1	6.0	8.6	6.0	8.7	9.0	24.0	0	..	8.8
Females:												
Autopsy performed in all cases	8	25	74	177	227	228	278	245	126	12	12	1,412
Subdural hemorrhages	0	0	2	10	18	11	29	19	6	2	0	97
Incidence of subdural hemorrhage, percentage	0	0	2.7	5.6	7.9	4.8	10.4	7.8	4.8	16.6	0	6.9
Total males and females:												
Autopsy performed in all cases	35	68	172	397	540	562	619	446	197	16	28	3,100
Subdural hemorrhages	1	3	7	24	45	44	59	37	23	2	0	245
Incidence of subdural hemorrhage, percentage	2.9	4.4	4.0	6.0	8.3	7.6	9.5	8.2	11.7	12.5	..	7.9

TABLE 2.—*Incidence of Types of Psychosis in Which Subdural Hemorrhages Occurred*

Order of Rank	Psychiatric Diagnoses	Actual No. of Cases in Which Autopsy Was Performed	Actual No. of Subdural Hemorrhages Found	Estimated No. of Subdural Hemorrhages That Might Be Found per 1,000*	Percentage	Order of Rank
1.	Dementia praecox	576	35	61	6.1	7
2.	Psychosis with cerebral arteriosclerosis	417	43	103	10.3	4
3.	Senile psychosis	413	36	87	8.7	5
4.	Dementia paralytica	338	35	104	10.4	3
5.	Psychosis with mental deficiency	234	11	47	4.7	8
6.	Alcoholic psychosis	192	16	83	8.3	6
7.	Epileptic psychosis	178	22	124	12.4	2
8.	Manic-depressive psychosis	171	8	47	4.7	9
9.	Psychosis with somatic disease	158	3	19	1.9	11
10.	Undiagnosed psychosis	116	3	26	2.6	10
11.	Psychosis with other disease of the brain and nervous system	101	16	159	15.9	1

* Assuming that autopsies were performed in 1,000 cases of a stated psychosis (based on incidence among actual numbers in this series).

Final Order of Rank †

		Estimated. No. per 1,000 Autopsies
1.	Psychosis with other diseases of the brain and nervous diseases	159
2.	Epileptic psychosis	124
3.	Dementia paralytica	104
4.	Psychosis with cerebral arteriosclerosis	103
5.	Senile psychosis	87
6.	Alcoholic psychosis	83
7.	Dementia praecox	61
8.	Psychosis with mental deficiency	47
9.	Manic-depressive psychosis	47
10.	Undiagnosed psychosis	26
11.	Psychosis with other somatic disease	19

† Based on estimated number of subdural hemorrhages found per 1,000 autopsies in cases of a given psychosis.

These varied in consistency from fresh blood to extreme states of calcification. Intermediate states predominated, i. e., organized membrane formations and subdural cysts. In most cases there was reason to believe that the psychosis was not caused by the subdural hemorrhage but that it was more probable that the hemorrhage occurred incidentally in the course of a psychosis. No single etiologic factor seemed of signal importance. The factors of atrophy of the brain, vascular disease and trauma were present frequently in combination.

DISCUSSION

DR. T. J. PUTNAM: It is extraordinary that this relatively common and characteristic lesion, which has been recognized for several centuries and of which there are perhaps a thousand case reports in the literature, should still be so unfamiliar to most physicians. The fact that it occurred in 6 per cent of the patients studied testifies to its importance; yet few textbooks of medicine devote more than a paragraph to it, and that is usually inaccurate.

Several points in the pathologic process of the disease particularly interest me. One is, how does the original hemorrhage occur? A few years ago, when I investigated the subject the question seemed to me unsolved. Since then, Dr. Timothy Leary has demonstrated clearly in several cases that the source of blood

TABLE 3.—*Causes of Death in 245 Cases*

Death Due to	No. of Cases
(a) Diseases of the central nervous system	117
(b) Diseases of the respiratory system	87
(c) Diseases of the cardiovascular system	66
(d) Fractures	45
(e) Miscellaneous causes	31
(f) Diseases of the genito-urinary system	17
(g) Diseases of the gastro-intestinal system	16
Total causes of death in 245 cases	379

was a ruptured vein running between the pia and the dura. The early increase in the size of the lesion is probably due to osmosis of spinal fluid into the cyst, as pointed out by Gardiner, and Fremont-Smith has suggested that this in turn is due to breakdown of the proteins of the blood. In addition, there appears in some instances to be a late increase in size, sometimes as late as two years after the original trauma. I wish to ask Dr. Moore if he has any evidence that secondary hemorrhage may occur, as has been my belief.

DR. M. MOORE: It would be difficult to say much definitely about the etiology of the psychoses. The subdural bleeding may have been a factor in producing the psychoses, particularly in the cases of arteriosclerosis. As to whether or not this is true, I cannot say because of lack of detailed information in individual cases.

There is evidence that bleeding occurs more than once, and in several of the specimens there were layers of bleeding that showed different degrees of fibrosis.

THE PSYCHOGALVANIC REFLEX: APPLICATIONS TO NEUROLOGY AND PSYCHIATRY. DR. PHILIP SOLOMON.

This article was published in the October 1935 issue of the ARCHIVES, p. 818.

SOME DYNAMIC ASPECTS OF DEMENTIA PARALYTICA. DR. MORRIS YORSHIS.

According to Dr. H. C. Solomon, the final prognosis in many cases of dementia paralytica depends on the amount of damage that has occurred before the activity of the pathologic process has been therapeutically arrested. It is my opinion that the prognosis depends also on the heredity and the constitution of the patient plus his ability and inability to make an adjustment in the social, economic and sexual

spheres prior to the onset of dementia paralytica. The history before the onset of the disease, results of mental examination, clinical course and treatment in 12 cases selected from 75 were discussed. It is logical to infer from the material presented that the premorbid history is as important a prognosticator as the age, onset, duration and clinical type. In the study of dementia paralytica and the treatment to be applied, the life history should be investigated in as detailed a manner as in the cases of functional psychosis.

DISCUSSION

DR. H. C. SOLOMON: Dr. Yorshis has taken an interesting approach to the question of prognosis in dementia paralytica following treatment. I think that it must be borne in mind that, as he has emphasized, this is a preliminary statement; with any criticism that I may offer I realize that as the investigation progresses it may become meaningless. First, I note that in cases 2, 3 and 4, in which bad results were obtained, the patients were given neither fever nor tryparsamide therapy but only a type of treatment from which there is little reason to expect improvement. Therefore, I do not think one can justly use these cases in the present consideration.

There were also several patients with definitely schizophrenic syndromes. Almost every one has recognized that a person with dementia paralytica with this syndrome does not do well; although the process of dementia paralytica may be healed, one still has the picture of the schizophrenic psychosis.

Finally, I was not convinced by the charts as to how much significance should be attached to some of the personality traits antedating the dementia paralytica. For example, there were two patients in whom "seclusiveness" was mentioned. In one, this seclusiveness was considered as having great importance in indicating a bad prognosis, whereas in the other it seemed to have little prognostic value from Dr. Yorshis' point of view and the patient recovered.

In conclusion, I say again that it is an interesting approach which should be followed through.

DR. H. R. VIETS: It is always good to see the bad results which occur in cases of neurosyphilis in spite of modern treatment. One is always surprised, on the other hand, to find how many patients recover from neurosyphilis without any treatment at all. It is not uncommon to find examples of so-called "burnt-out" tabes in patients who have cured themselves without the benefit of antisyphilitic drugs. There are, therefore, other factors that must be considered when one surveys the results of treatment of neurosyphilis. One of these factors has been strongly emphasized by Dr. Yorshis.

DR. A. H. RUGGLES: I wish to call attention to the need of a more thorough approach in taking the history in these cases. There is danger of not securing a sufficiently accurate history. One should be careful to emphasize this. One branch of the family may give one type of history, and another branch, a very different one.

DR. J. LOMAN: Has Dr. Yorshis any control group of cases? In other words, how many patients with an unfavorable past history showed improvement due to antisyphilitic treatment? It is probable that the study of a large number of patients by Dr. Yorshis' method is necessary before the results can be better evaluated.

DR. JEROME WHITNEY: Did not ignorance and neglect cause a delay of treatment in this group with the unfavorable past history?

DR. C. A. MCDONALD: I was impressed by the age of the patients—some were 27, 28 and 30. I was under the impression that dementia paralytica does not commence so early.

DR. D. J. MACPHERSON: This line of approach may be of help in predicting the results of therapy. It would be interesting to correlate the relation between these facts and the serologic reactions. Was this relation followed in the group studied?

DR. I. CORIAT: In anticipation of the title of Dr. Yorshis' paper I jotted down a few notes from a paper of mine which has remained unpublished and which was read at the 1933 meeting of the American Psychiatric Association in opening a round table discussion on psychoanalysis and psychiatry. The paper covered the subject of the mental symptoms of dementia paralytica, and it might have some bearing on the subject at hand. In 1922 Ferenczi and Hollos published a monograph on dementia paralytica, with particular reference to the psychology of deterioration and the psychogenesis of individual symptoms of this condition. Organic diseases may have special points of attack on psychologic systems, and many of the symptoms evolved depend on parts of the body highly prized by the ego. Ferenczi thus postulated a cerebral pathoneurosis to explain the symptomatology of dementia paralytica as an addition to the descriptive level. The clinical outlines of three cases of dementia paralytica were presented in my paper.

1. A patient with the tabetic form of dementia paralytica had a delusion of infection six weeks previously. The existence of original infection was denied; its remote origin was repressed owing to a feeling of guilt from the super-ego.

2. A patient with very marked dementia underwent regression to infantile activities.

3. A patient had extensive delusions of grandeur which were merely fantasies substituted for what had been lacked in reality.

It seems from other material, as Dr. Yorshis has pointed out, that the prepsychotic history is, as in all functional diseases, of paramount importance and should be made a subject of extensive study from the standpoint of the personality.

DR. M. YORSHIS: Malaria, tryparsamide and diathermy have been used in some cases without improvement. Dr. Ruggles' point is well taken. I confess that the histories in cases of dementia paralytica in state hospitals are inadequate. If the spinal fluid gives a positive reaction for dementia paralytica, treatment is started and the premorbid status is not investigated carefully. In reply to Dr. Loman's question about the control group, I have yet to see a patient with a poor premorbid history improve to the point where he could leave the hospital and be self-supporting. This is only a preliminary report. More definite statements will be made when the series is of statistical significance.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 21, 1935

THEODORE T. STONE, M.D., *President, Presiding.*

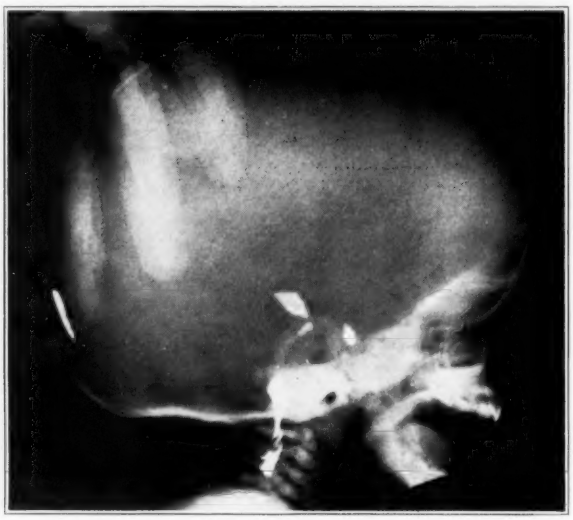
VENTRICULOGRAPHY WITH COLLOIDAL THORIUM DIOXIDE AS A CONTRAST MEDIUM. DR. WALTER FREEMAN, Washington, D. C. (by invitation).

Colloidal thorium dioxide is freely miscible with the cerebrospinal fluid and is of high specific gravity and great radiopacity, three features which render its use in the delineation of the cerebral ventricles of exceptional value. Moreover, it is relatively nonirritating, giving rise to little cellular reaction in the meninges aside from the macrophages, which are present in large numbers. In cases in which there is no obstruction of the ventricular system the material is entirely eliminated in from two to four hours, presumably through the arachnoid villi. However, in cases of obstruction some of the material can be found at least ten days after its injection. Two cubic centimeters of the material is introduced into each lateral ventricle, an effort being made to mix the material with the ventricular fluid as thoroughly as possible. The roentgenograms reveal with remarkable clarity all the various nooks and crannies of the ventricular system, and by means of this I have been able to localize accurately two tumors of the posterior fossa. The material has been used in twelve cases during the last eighteen months with-

out a death and with only two rather severe reactions, consisting of fever, stiffness of the neck and severe headache. Patients presenting no obvious lesions have been able to leave the hospital in four days.

DISCUSSION

DR. PAUL C. BUCY: This method will be of assistance in many cases in which there is difficulty in making satisfactory ventriculograms. In cases in which the ventricles are small it is often difficult to obtain satisfactory pictures with the injection of air. The use of colloidal thorium dioxide will simplify that problem. I have not used thorium dioxide, but in some children with obstructive hydrocephalus in whom I have found difficulty in localizing the obstruction I have used iodized poppy-seed oil 40 per cent to demonstrate the point of obstruction, as seen in the accompanying figure. I do not believe that this substance has the adaptability of thorium dioxide which Dr. Freeman has demonstrated.



Roentgenogram showing congenital obstructive hydrocephalus. The fourth ventricle is clearly outlined by iodized oil originally placed in the lateral ventricle. The obstruction is seen to lie not at the foramina of the fourth ventricle but in the upper part of the cervical portion of the cord. Iodized oil is also seen in the lateral and third ventricles.

DR. HANS H. REESE: During the past three years many reports on the use of thorium dioxide for the visualization of the spleen, liver, blood vessels and kidneys have appeared. Thorium dioxide has replaced sodium iodide in arteriography of the brain (Moniz, Jacobi and Loehr, then Schaltenbrand and Jessen), and no complications have been recorded. Dr. Freeman's excellent ventriculograms made with thorium dioxide as a contrast medium and his clinical observation with pathologic investigations demonstrate the value of this new and apparently not hazardous procedure.

I have not seen any irritating effects from the use of thorium dioxide. (A few patients have been subjected to the intracarotid injection of thorium dioxide, and only one cyst of the brain has been distinctly outlined with this contrast medium.) Histologic studies of the liver, spleen and bone marrow in over 80 rabbits following the intravenous injection of thorium dioxide by Pohle and Ritchie at the University of Wisconsin, with an observation period of four

hundred and ninety-three days, revealed that the radiopacity in the spleen remained manifest during the entire period of observation. Thorium dioxide is deposited in the reticulo-endothelial cells of the liver, spleen and bone marrow in fine granules. Whereas the bone marrow undergoes hyperplasia early, followed by partial disappearance of the blood-forming centers and serous atrophy of the fat, the liver presented hydropic degeneration, edema of the portal spaces and dilatation of the periportal lymphatics. Later, just as in the spleen, slight fibrosis was seen in the liver.

I wish to ask Dr. Freeman two questions: Has he observed any clinical manifestations as to changes in the blood picture, in the hepatic function and in the size of the spleen? How soon after the administration of thorium dioxide must roentgenograms be taken?

Dr. Loyal Davis: Mechanical methods of localizing intracranial tumors, such as pneumography and the introduction of thorium dioxide, are of great value in many cases, but I believe the frequency with which they are used depends largely on the amount and character of clinical study applied in the case. One of the greatest dangers in encephalography or ventriculography is the use of the method by some one who is not prepared to operate immediately in the case of a catastrophe. All neurologic surgeons have had the experience of making an encephalogram or a ventriculogram and later finding it necessary to operate at once because of the reaction which occurs. It is difficult for a roentgenologist to interpret encephalograms and ventriculograms without having the added knowledge which comes to the surgeon as he performs these procedures. Consequently, I believe that in most instances the surgeon is better able to interpret pneumograms than is the roentgenologist.

Dr. Freeman has not used thorium dioxide in many patients with space-occupying lesions, so he is not prepared to state what may happen in the case of a severe obstruction to the cerebrospinal fluid. Naturally, this is a point in which lies the most interest. Encephalography and ventriculography properly done afford much information, but the greatest value of these procedures has been in the localization of intraventricular tumors. In the presence of an apparent deformity of the ventricular system, as shown by an encephalogram or a ventriculogram, it is the rule that a carefully made and often repeated neurologic examination yields symptoms of definite and positive localizing value. Many things can be learned about the ventricular system without the introduction of air or any other medium.

I believe that the use of thorium dioxide is an interesting step in the development of mechanical aids in the diagnosis of intracranial lesions, but it should be used with care. From this presentation I do not see any great advantage in the use of this medium over the use of air.

Dr. Arthur Weil: Dr. Freeman pointed out that the question of whether following the introduction of thorium dioxide there may not be an inflammatory response of the pia-arachnoid with an increase of fibroblasts and connective tissue fibers is not settled. Even following hemorrhages into the subarachnoid spaces there occurs, together with the removal of the red blood cells and their débris by scavenger cells, a mild increase in fibroblasts and collagenous connective tissue fibers, which leads to thickening of the pia-arachnoid and to adhesions. If invasion of cells of the body itself into the subarachnoid spaces leads to such a marked response, how much more inflammatory reaction must one expect following the introduction of foreign bodies like thorium dioxide. Therefore, one should be careful in stating that such a method is harmless and should await the outcome of experiments on animals before drawing definite conclusions.

Dr. Walter Freeman: The question of the harm that thorium dioxide can do in the body is, I think, answered by the fact that five or more years ago the Germans began injecting this material intravenously; it has been used in Washington in doses as high as 75 cc. for demonstrating the liver and spleen. Patients who did not have serious disease of the spleen or liver have normal function. Whether this would be true of the brain I cannot yet say. I have made histologic

examinations in three cases and have found very few lymphocytes but a large number of macrophages containing the thorium dioxide. I think one can appreciate that the reaction from thorium dioxide is entirely different from that due to blood cells. Subarachnoid hemorrhage provokes much exudate, with leukocytes and lymphocytes, and when there is also occlusion of the arachnoid villi a condition may develop that may interfere with resorption of the thorium dioxide. It was only in cases in which the needle went astray that my colleagues and I obtained these pictures of the cortical fissures both roentgenographically and histologically.

The use of iodized oil is indicated in some cases, particularly in a study of the spinal cord, but I do not see that it can offer much information in the ventricular region.

Taking the pictures within one-half hour is satisfactory, but if one waits two hours the medium may be eliminated. The roentgenogram need not be taken on the operating table. So far catastrophies have been avoided, and there has been no complaint of pain at any time, the procedure differing in this respect from pneumoroentgenography. The work is always done by a surgeon, and my associate, Dr. Schoenfeldt, is always ready to operate at a moment's notice. Serial roentgenograms show that the material after being injected goes rapidly through the fourth ventricle and out into the subarachnoid space in cases in which there is no obstruction. One can find macrophages containing thorium dioxide in the cerebral sulci after the material has been injected into the spinal canal.

ON INTRAVENOUS INJECTIONS OF HYPOTONIC AND HYPERTONIC SOLUTIONS: THEIR THERAPEUTIC VALUE IN THE TREATMENT OF SOME MENTAL CONDITIONS. DR. GEORGE B. HASSIN and DR. SAMUEL B. BRODER. (by invitation).

Assuming that the clinical manifestations of dementia praecox are due either to excessive accumulation of toxic catabolic substances or to their deficient elimination, we thought it advisable to determine whether forced elimination of such problematic substances (by washing them out) would not favorably affect the clinical picture. By utilizing the method of Weed and his co-workers, it is possible to flood the brain tissues by intravenous injections of hypotonic salt solutions. The excessive amounts of fluids thus produced and containing waste products of the brain tissues can be removed to the blood vessels or their adventitial spaces by subsequent intravenous injections of hypertonic salt solutions. In some instances we combined the injections with continuous or forced drainage, as used by Kubie and others. The injections were given every five or eight days for a period (in one case) of nine months; the hypotonic solution used was a 0.4 or 0.2 per cent solution of sodium chloride (as much as 2,225 cc.); the hypertonic solution was a 10 per cent solution of magnesium sulphate (25 cc.). No striking changes were noted in the blood count, temperature, respiratory rate, chemistry of the blood and spinal fluid, etc. The mental condition exhibited very slight transient improvement. We planned to use this method on a large group of patients, but we discontinued it after a careful trial on 3 patients proved it to be worthless. The cause of the failure, in our opinion, is the impossibility of washing out all the toxins or even a major portion of them and of preventing their new formation.

DISCUSSION

DR. GEORGE B. HASSIN: A full report of our experience with intravenous injections is to appear in *The Journal of the American Medical Association*. So far only persons with various types of meningitis and some degenerative conditions of the central nervous system (multiple sclerosis) have been treated with injections of hypotonic salt solutions. We thought it worth while to try the method in the treatment of mental disorders, and we chose patients with catatonic dementia praecox as the most suitable for our experiments. Unfortunately, the results so far were insignificant.

DR. HARRY A. PASKIND: I wish to ask Dr. Hassin the name or nature of the toxin that is being washed out of patients with dementia praecox.

DR. BENJAMIN BOSHES: I wish to know if there is any proof that the solution actually washed the brain tissue. My colleagues and I had an interesting experience with animals, studying halides in the various organs. We found that there was only about 160 mg. per hundred grams of sodium chloride in the brain, whereas in the blood there was 500 mg. The more completely we exsanguinated the brain, the less sodium chloride we found. The sodium chloride is fairly tightly bound. We do not know of any proof that a substance going through the blood vessels of the brain actually enters brain tissue. Unless the latter occurs, how can one "wash the brain?"

DR. SAMUEL B. BRODER: I mentioned in the paper that the duration of the injections was from one to two hours and the amount from 1,500 to 2,500 cc. As to concentration, we used solutions of as low as 0.2 per cent, and there was no danger in doing that. We always inserted the needle for lumbar puncture first and then the needle for intravenous injection.

The aim in this work is to render the blood hypotonic, and this may be accomplished either by the intravenous injection of strongly hypotonic salt solution or by the administration of large quantities of water by mouth. However, in the latter case prompt diuresis ensues, and as a result of this the dilution of the blood is only slight. To prevent diuresis temporarily, Motzfeld suggested that an injection of solution of pituitary precede the injection of water. Kubie quoted Spurling and others, who have given as much as 7 liters of water by mouth per day; in order to check the excretion of urine some used pitressin and thus rendered the blood hypotonic.

DR. GEORGE B. HASSIN: Dr. Paskind knows that I am not a chemist and that I cannot give the names of the chemical substances, designated by me problematic toxins, which are discharged into the subarachnoid space. I do not know whether it is important for our purposes to know the exact names of the toxins.

As to Dr. Boshes' statement, it is immaterial how much sodium chloride reaches the brain. It is the hypotonic feature of the fluid injected and its ability to cause edema of the brain tissues that are of importance. Ordinary distilled water has the same effect. I do not know how much of the saline solution injected reaches the brain or how much of it escapes to the subarachnoid space. That is immaterial; but observations made by us were considered of sufficient interest to be recorded, as they may be of help to future workers with similar methods.

GALVANIC SKIN REFLEX AND DANIELOPOLU TEST IN PSYCHONEUROTIC PATIENTS. DR. THOMAS L. FENTRESS and DR. ALFRED P. SOLOMON.

This paper will be published in full in a later issue of the ARCHIVES.

PHILADELPHIA NEUROLOGICAL SOCIETY

Feb. 22, 1935

FRANCIS C. GRANT, M.D., *President, in the Chair*

STRIATAL MANIFESTATIONS FOLLOWING DIPHTHERIA. DR. ALFRED GORDON.

The study of epidemic encephalitis has furnished a strong impetus for a closer investigation of the manifestations of cerebral involvement occurring in many infectious diseases. The clinical picture of invasion of the nervous system is polymorphic. Indeed, sometimes the phenomena are those of encephalitis and sometimes of meningo-encephalitis, myelitis, hydrocephalus, multiple neuritis or

even poliomyelitis. Among these complications, encephalitis, however, is the most frequent and presents chiefly a diffuse involvement with clearly defined localizations. There are many varieties of the infectious insults in the brain, especially in children. The lesions are small hemorrhages, cerebral edema or venous thrombosis. No particular forms of encephalitis are specific for the infectious diseases. In the majority of cases the outcome is favorable, particularly in children, with no sequelae. Occasionally and rarely the extrapyramidal system may be involved. The case to be reported is an example of one of the postencephalitic sequelae of the parkinsonian type, which followed an attack of diphtheria.

The frequency of encephalitis in the course of, or following, infectious diseases suggests the possibility of an ultravirus as the etiologic factor in the causation of encephalitis. The microscopic picture differs decidedly from that of epidemic encephalitis and from that of anterior poliomyelitis.

The case to be reported is that of a woman, aged *22*, who had an attack of typical diphtheria three years before. She recovered completely after one month. Shortly afterward abnormal movements began in the extremities and became gradually more pronounced. There is a typical parkinsonian facies: The eyes are widely open, there is immobility of the muscles, the whole face is drawn and emotional expression is poor. Both hands show a passive tremor, more on the left than on the right, which is more pronounced on voluntary movement. There are very fine myoclonic contractions of some muscles, especially in the legs. There is some ataxia in the left hand. Hyperkinesia, with which the entire body is affected, is conspicuous. In standing the patient shifts constantly, putting her entire weight first on one foot and then on the other, and she sways from side to side. In sitting she changes the position of her legs continually, crossing one over the other and then back again an indefinite number of times. Examination reveals no special somatic abnormalities. The reflexes, sensation, sphincters, pupillary reactions, blood, urine and spinal fluid are all normal. Mentally the patient is somewhat below normal; at the age of 15 she was only in the sixth grade. She never cared to associate with others. She has no objective in life. Her sole desire is to remain with her mother. She is supremely contented. She was born at term, walked and talked at the age of 2½ years and had whooping cough at the age of 4 months. There were no other infectious diseases.

DISCUSSION

DR. F. H. LEWY: Globus described a case a long time ago in which he found diphtheria bacilli in the meninges. It is interesting that Dr. Gordon's case was one of hypermotility. Twelve years ago I found that choreiform restlessness developed in mice infected with diphtheria bacilli of certain strains. Histologically, in these mice a degeneration of toxic type was present in the small ganglion cells of the putamen.

SYNDROME REFERABLE TO THE CAUDA EQUINA FOLLOWING THE INTRASPINAL INJECTION OF ALCOHOL FOR RELIEF FROM PAIN. DR. PAUL SLOANE.

H. Y., a man aged 46, a truck driver, was admitted to the medical service of Dr. Corrigan at St. Joseph's Hospital, Reading, Pa., in November 1934, with a history of having suffered from severe abdominal pains for a year. The pain came in paroxysms and could be precipitated by exertion or by violent coughing or sneezing. It was described as sharp and shooting and was referred to the epigastrium, whence it would radiate along the costal margins bilaterally. It was usually associated with nausea. Each paroxysm lasted for several hours. The pain was so severe at times that it threw the patient to the floor in agony, and on one occasion he fainted. It could be controlled only with large doses of morphine. In June 1934 the patient was subjected to an operation for gastric ulcer, but no pathologic condition was found. A Wassermann test of the blood at that time was positive. He subsequently received antisyphilitic therapy (bismuth preparations and

neoarsphenamine) for several months with no relief. He was readmitted to the hospital on November 24 for the same complaint.

On examination he appeared to be in great pain. He showed some memory defect and could not repeat four given numbers in reverse. The pupils were equal but slightly irregular. They reacted somewhat sluggishly to light, but promptly on convergence. In carrying out commands there was overaction of the muscles of expression. Speech was slurring. Both hands showed coarse tremors. The deep reflexes were exaggerated but equal. The abdominal reflexes were active and equal. The plantar responses bilaterally were neutral. Pressure on the ulnar nerves and achilles tendons caused no pain, although the testes were sensitive. There was hypalgesia along the ulnar borders of both hands and forearms and in the region of the nipple. There was a belt of hyperesthesia at the level of the epigastrium. The Romberg sign was present although no signs referable to the posterior columns could be detected on gross testing. The Wassermann reaction of the blood and spinal fluid was positive. The colloidal gold curve was 122332100. A diagnosis of the tabetic form of dementia paralytica with gastric crises was made.

With the patient lying on the left side, a lumbar tap was done between the third and the fourth lumbar vertebra, and 1 cc. of absolute alcohol was injected by barbotage. After the injection the patient had no more pain. On the following day, however, he complained that he could not void urine or move his bowels. Catheterization was instituted. Examination at this time revealed absence of the right ankle jerk, with moderate weakness in the dorsiflexor, invertor and evertor muscles of both feet, which was more marked on the right. There was absolute anesthesia in the perianal region on the right, extending down the back of the thigh and leg. On the left, there was diminution of sensation in the same distribution. The patient stated that he felt the passage of urine and of the catheter. These signs pointed to involvement of the cauda equina, particularly on the right side. Cystitis developed, with severe pains in the region of the bladder, which cleared up gradually. After a week there began dribbling of urine instead of retention, and the bowel movements became more free. When last examined (Feb. 16, 1935) the patient had fairly good control of the bowels except for some degree of urgency; if he did not go to the stool at once he soiled himself. He required a laxative every other day. He could urinate without difficulty as a rule, although at times there was some delay in starting the stream. There was still some nocturnal incontinence. He also complained of numbness along the back of the right thigh. He stated that he had had no abdominal pain since the injection was performed. Examination showed the following changes: The ankle jerk on the right could be brought out on reenforcement; there were hypesthesia and hypalgesia, instead of anesthesia, in the entire sacral distribution on the right, but only in the perianal zone on the left; some weakness of the feet persisted. The patient was entirely comfortable. He stated that it was worth going through this trouble to be rid of the pain.

The first reports on the use of intraspinal injections of absolute alcohol for relief from intractable pain were published in 1931 by Dogliotti. He, as well as most writers on the subject, was aware of the possible dangers attendant on the use of this method. Kafer and Sanguinetti reported a case of sciatica in which the patient was treated by the intraspinal injection of 0.2 cc. of a 25 per cent solution of antipyrine in 80 per cent alcohol. There developed immediately a typical syndrome of conus medullaris, with retention of urine and feces, which cleared up gradually within seven months.

In the case presented the lesion obviously extended beyond the distribution of the conus to involve the cauda equina. Involvement chiefly of the right side could be explained by the fact that the patient was lying on the left side during the injection, so that the spinal roots on the right side were uppermost. The alcohol, floating to the top, would naturally affect these roots. Alcohol produces a degenerative lesion of the spinal roots without affecting the afferent pathways in the cord, according to Stern. It is therefore likely that the cauda equina rather than

the conus was involved also in the case reported by Kafer and Sanguinetti, particularly in view of the comparatively rapid recovery. The amount of alcohol used in the case reported here (1 cc.) was the maximum suggested by Dogliotti. Had a smaller dose been used it is possible that complications would have been avoided.

DISCUSSION

DR. BERNARD J. ALPERS: I recently studied a case of metastatic carcinoma involving the spinal cord in which the patient had had subarachnoid injections of alcohol a sufficiently long time previously to make histologic studies valuable. One injection was made into the lumbar region and one into the thoracic region. In the cauda equina there was definite degeneration of the roots, also degeneration of the axis-cylinders. There were secondary changes in the spinal cord consisting of degeneration of the spinocerebellar fibers. In the thoracic region there was degeneration not only of the posterior roots but also of the anterior roots. A few anterior horn cells showed degeneration. I think that the claims that alcohol does not diffuse are not entirely in accord with the facts, for I found changes not only in the upper part of the spinal cord but also in the lower part. There seems to be some damage of the spinal cord with these injections, and I think that Dr. Sloane's warning that treatment as radical as this should be reserved for hopeless conditions, or for conditions in which there is no possibility of relief by other means, is a good one.

DR. FRANCIS C. GRANT: Was there relief from pain in this particular case?

DR. BERNARD J. ALPERS: There was complete relief from pain.

DR. FRANCIS C. GRANT: What does Dr. Sloane mean by barbotage?

DR. PAUL SLOANE: The procedure consists in mixing spinal fluid with alcohol and then reinjecting it.

DR. FRANCIS C. GRANT: I suspected that that was the meaning. Both Stern and Elson warned against this procedure. They said that the alcohol should be injected directly, without mixing. They claimed that in this way there is more direct action on the roots as well as less diffusion of the alcohol. I have used injections of alcohol in 4 cases of a malignant growth in the pelvis; in 3 there was relief from pain, in one patient for five months, in another for six and in a third for three. There has been sufficient relief from pain to omit all opiates; acetylsalicylic acid has been sufficient to control any distress. There has been no sphincteric or motor involvement following any of the four injections. The fourth injection was not successful. I feel a little more optimistic about the method than I think Dr. Sloane or Dr. Alpers does. An attempt was made in all 4 cases to inject the alcohol between the second and the third lumbar vertebra. The injections were of 1 cc. of absolute alcohol, the patient's hips being kept well up and the injection being made very slowly; the patient was kept in this position for three quarters of an hour or more and then turned on the back with the feet higher than the head. The treatment in this case was done for relief from pain in the pelvis or down the leg. In the 4 cases the pain was unilateral, and in 3 cases it extended down the leg.

DR. PAUL SLOANE: How does Dr. Grant explain the absence of sphincteric disturbance?

DR. FRANCIS C. GRANT: I cannot explain it. One woman had some difficulty in urination for forty-eight hours, but not sufficient to require catheterization.

DR. ALFRED GORDON: In carrying out nerve block in other parts of the body I have obtained considerable relief by the injection of 70 per cent alcohol. Would it not be advisable to try this modification of the technic? It is possible that some of the poor results described have been due to the use of 100 per cent alcohol. It may be that 70 per cent alcohol would give as much relief with less chance of paralysis.

DR. ALEXANDER SILVERSTEIN: I gave one subarachnoid injection of alcohol a week ago. The patient, a woman aged 70, had had tabes dorsalis with gastric

crises and severe lancinating pain in the lower limbs for twenty years. The pains were so severe that hypodermic injections of ½ grain (0.032 Gm.) of morphine sulphate failed to give relief. The family physician had already promised the patient that she would be cured if the injection was given, and it was therefore not a matter of deciding on the advisability of the procedure but of carrying it out successfully. Nine cubic centimeters of absolute alcohol was injected slowly into the subarachnoid space. At the beginning, when only a few drops had been injected, the patient complained of severe pain in the toes of the right foot, which gradually ascended to the midthigh. Following the injection the patient had motor and sensory paralysis of the right lower extremity. After six hours she was able to move the leg. The pain disappeared, and she was fairly comfortable, except for attacks of vomiting. Forty-eight hours after the injection there developed symptoms from an incarcerated hernia for which an operation was performed. I think that injection of alcohol into the subarachnoid space should be used only in cases in which chordotomy is seriously considered. The patient should be informed of the possibility of paralysis of the extremities.

Dr. Francis C. Grant: How many injections have been given in the University Hospital?

Dr. Stuart N. Rowe: Three cases have been observed recently in the University Hospital, and my associates and I have been impressed with three things. First, pain can be relieved by this method. Two patients had direct involvement of the nerves close to the spinal cord, so that they were suffering from severe pain. One patient, a girl with sarcoma, has been relieved for a month, although the pain had been so severe that she had taken morphine two and three times a day. Second, the procedure may be dangerous. The second case was one of carcinoma of the vulva; after the injection of 1 cc. of alcohol complete loss of control of both bladder and bowel sphincters was noted. Fortunately, that disappeared in the course of two weeks. Another evidence of the dangers of the procedure is that changes in the spinal cord cells occur, as shown by Dr. Alpers in the spinal cord removed in another case. Third, it may well be possible to avoid some of the dangers of this procedure by giving smaller doses of alcohol and, if necessary, repeating them if the first injection is not followed by relief from pain.

Pseudotumor Cerebri. Dr. Alexander Silverstein.

It is well recognized that pathologic conditions other than tumor may produce all the clinical features of the "tumor syndrome" in the brain and the spinal cord. Hughlings Jackson in 1876 described the clinical picture of tumor of the brain in a case in which at necropsy there was only congestion of the brain. Quincke described similar cases under the title of serous meningitis. In this country Spiller, under the title of circumscribed serous spinal meningitis, reported a case presenting the characteristic clinical features of a tumor of the spinal cord. Operation resulted in complete cure. More than six years later the patient was still free from all symptoms. This, the first case on record in which operation was performed, aroused great interest by calling attention to this type of change in the membranes of the spinal cord and the brain.

The term pseudotumor as applied to cerebral lesions was first introduced by Nonne in 1904. His insistence that in a number of cases no microscopic pathologic changes in the brain could be found to explain the clinical picture has given rise to considerable discussion in the literature. Bailey in 1920 criticized the findings of Nonne after analyzing the latter's cases and those in the literature and concluded that the term pseudotumor cerebri, if it is to be used at all, "should be restricted to purposes of clinical classification without attributing to it any pathological or etiological significance whatever." Frazier in 1930, in a comprehensive review of the subject, accepted the term pseudotumor and pointed out that the condition has been referred to in the literature by various names, such as meningitis serosa, arachnitis, meningo-encephalitis, serous infusion of inflammatory origin and generalized cisternal arachnitis. In his series of 22 cases, 19 patients were alive after

a period varying from one to twenty-five years. He classified his cases according to the localizing symptoms; for example, a group with symptoms pointing (1) to the motor cortex, (2) to the posterior fossa, (3) to a cerebral hemisphere and (4) to the base of the brain. Of special interest is his report of the case of a patient showing a syndrome indicative of cerebellar involvement with a swelling of the disks of + 11 diopters. After surgical exploration the patient's condition improved and he remained free from symptoms for twenty-five years. This group of cases with symptoms referable to the posterior fossa was well reviewed in 1924 by Horrax, who reported 33 cases. Of particular interest also is the fourth group in Frazier's series, consisting of 4 cases in which there were changes in the visual fields and symptoms indicating a lesion of the pituitary gland. This group has received considerable attention in the literature. Davis and Haven emphasized that the changes in the arachnoid, both in the cerebral and in the spinal form of arachnoiditis, closely resemble those seen in the vicinity of tumors, so that a lingering suspicion of the presence of tumor should be entertained in every case in which the condition seen at operation is the only lesion detected. They believed that all these cases should be classified as "tumor suspects" rather than as cases of arachnoiditis or pseudotumor.

The following case is reported because it has given the opportunity to follow up a patient who at one time showed the characteristic clinical features of a "brain tumor syndrome." Although all the symptoms disappeared, the case was considered suggestive of tumor. While under observation the patient contracted tetanus. Necropsy failed to reveal a mass lesion.

W. B., a man aged 46, was admitted to the service of Dr. J. O. Bower, at the Temple University Hospital, on Sept. 14, 1933, with the complaint of headache and projectile vomiting. He had been in fairly good health up to January 1933, when he became markedly depressed, had loss of appetite, insomnia and periods of mild agitation and suffered from what his wife referred to as "an unnatural type of grief." During this period he complained of pressure in the head, which at times developed into severe paroxysms of pain. There were no other complaints until three weeks prior to his admission to the hospital, when he was found unconscious at work, with his lip cut and the left eye discolored. Following this attack of unconsciousness, the duration of which is not known, he had severe headaches and projectile vomiting and was mentally confused. After ten days of treatment at the Joseph Price Hospital he was discharged with some improvement in all symptoms.

At home the patient was fairly comfortable for a week, when he suddenly had another convulsive seizure, seventeen days after the first seizure. An interesting occurrence during and following the convulsive seizure was unilateral sweating of the right side of the body, which was so excessive as to penetrate the mattress on that side. As in the previous attack this one also was followed by mental confusion, projectile vomiting and severe headache, localized mostly over the right eye. Two days after the onset of the second seizure the patient was admitted to the Temple University Hospital. A spinal puncture with the patient in the recumbent position was carried out by Dr. J. O. Bower, and the pressure was 30 mm. of mercury. The patient was transferred to the neurologic service of Dr. N. W. Winkelman.

The patient was still confused and complained of severe headache. The disks showed papilledema of 2 diopters in each eye. The left pupil was slightly larger than the right; both reacted to light and in accommodation. The external ocular movements were fairly good in all directions. There were some nystagmoid jerkings when the eyes were rotated laterally. The labiofacial fold on the left was slightly more flattened than that on the right, but both corners of the mouth could be drawn up equally well. The tongue protruded in the midline. The muscle power in both upper limbs was equal, the dynamometer recording 75 for each hand. There was no muscular weakness in the lower limbs. The biceps and triceps reflexes were active on both sides. The patellar and ankle jerks were hyperactive on both sides, but slightly more on the left. There was

an exhaustible ankle clonus on both sides, which was more sustained on the left. Plantar stimulation of the left foot caused no movement of the great toe, whereas on the right this caused flexion. The abdominal reflexes were absent on both sides. Vibratory sense was slightly diminished in both lower limbs. The senses of position and passive motion of the toes and fingers were preserved. Astereognosis was not present. Signs of meningeal involvement were absent. Examination of the spinal fluid on admission revealed 135 cells per cubic millimeter, with a predominance of lymphocytes; eight days later there were 75 cells per cubic millimeter and sixteen days after admission 81 cells. A culture of the spinal fluid was sterile; the Wassermann test was negative. Roentgenographic examination of the skull gave normal results. An encephalogram was made by Dr. Gotten on Sept. 30, 1933, sixteen days after admission; the spinal fluid pressure with the patient in the recumbent position was 6 mm. of mercury; 90 cc. of cerebrospinal fluid was removed, and 90 cc. of air was introduced. The interpretation of the plates by Dr. A. K. Merchant was as follows: "The lateral ventricles are entirely symmetrical and all of the ventricles are within normal limits of size. The midline structures are not displaced to either side. The only deviation from the normal is that there is no air in the cortex."

A Bárány examination on Sept. 26, 1933, by Dr. Winston suggested a supratentorial lesion on the right side.

On September 21, seven days after the patient's admission, the spinal manometric reading was reduced from 30 to 16 mm. of mercury, and on September 30, sixteen days after admission, to 6 mm. of mercury.

Examination of the fundus, which on two different occasions had been reported by Dr. Lillie as showing choked disk of 2 diopters with hemorrhages, gave normal results twenty-two days after admission. Almost immediately after the first spinal puncture there was prompt relief from the subjective symptoms of increased intracranial pressure. For a few days there appeared mild paresis on the right side with vasomotor and trophic changes, which, however, disappeared together with all the other symptoms. The patient was discharged from the hospital on December 10.

The patient was reexamined at regular intervals by Dr. Charles Barr, who found him to be in good health. On May 18, 1934, he sustained a compound fracture of the second and third fingers of the left hand; tetanus developed and he died.

The report of the microscopic examination of the brain by Dr. Winkelman was as follows: "Within the subarachnoid space one finds terrific dilatation and the presence of some free blood and considerable pigment. The amount of pigment here is greater than that usually seen, and fits in with the blood present within the subarachnoid space. There is a terrific congestion of all the blood vessels, with edema and marginal gliosis, with prominence of the small blood vessels, and with definite ganglion cell change.

"In the cornu ammonis there is an old area of softening that shows calcification and gliosis.

"Within the subcortex, one finds a status spongiosus of rather marked degree with an increase in the amount of glia of all types. There are collections of glia cell similar to what is seen in hemorrhagic foci. The motor cortex is rather interesting in that for the most part the Betz cells are richer in Nissl substance than the usual cell and they stain very heavily.

"Occasionally one finds a tendency to an axonal change, but this is not invariable. The large blood vessels show marked fibrosis, but nothing inconsistent with the age of about 50.

"The entire picture presented by the brain is that of severe irritation, with congestion and marked marginal gliosis. The Van Gieson preparations show the severe fibrosis that has occurred in the subarachnoid space."

Comment.—In reviewing the clinical picture in the light of the pathologic changes, this case obviously comes under the classification of pseudotumor cerebri. The most significant histologic change was severe fibrosis of the meninges.

There are a number of features in the clinical picture that deserve emphasis. First, the onset of the condition with symptoms of a mild psychotic nature and headaches of a neurasthenoid type were unusual. Psychotic manifestations have not been mentioned as significant symptoms in the recorded cases of pseudotumor. In this connection it is therefore pertinent to refer to an article by Claude, who called attention to the frequency of mental symptoms characteristic of true psychoses in these cases, particularly when the pathologic process affects the cerebral hemisphere. Claude also quoted Lewy, who emphasized that the type of headache in these cases is supposed to be characteristic in that it resembles that found in cases of neurasthenia and occurs in paroxysms of a migrainous nature.

The encephalographic report of absence of the cortical pathways deserves comment. An interpretation of this was, and still is, difficult to make. The first question on which to decide is whether the absence of the cortical pathways was due to an error in technic, such as incomplete drainage of the cerebral subarachnoid spaces, or whether this could be of any pathologic significance. Although it is difficult to come to a definite conclusion, one is tempted to consider the changes in the meninges as a causal factor. The evidence of the severe meningeal fibrosis would favor such a view. It must be added, however, that similar encephalographic findings have been reported in cases in which there was no cerebral pathologic process.

In contrast to the encephalographic findings in the case reported, it may be of interest to mention the changes described by Gardner in cases that presented a similar clinical picture. He designated a condition as active external hydrocephalus on the basis of the finding in the encephalogram of marked dilatation of the cerebral subarachnoid spaces with a normal ventricular outline. His 3 patients showed symptoms of high intracranial pressure, with a marked degree of choked disk. Subtemporal decompression produced prompt and permanent relief. The symptoms in Gardner's cases were similar to those in the case reported here. They differed in the encephalographic finding of the cortical air patterns. It may be mentioned that in the case reported here the encephalogram was made after the symptoms had abated, although the spinal fluid still showed a high cell count.

Another striking point in the clinical picture that concerns treatment in these cases was the prompt relief from all symptoms of increased intracranial pressure, including the psychotic manifestations, after spinal drainage and dehydration. In the literature there is a great difference of opinion as to the advisability of spinal drainage. While some investigators emphasize this procedure as a cure for the condition, others consider it of little value and also dangerous. I have seen 3 cases of pseudotumor in which spinal puncture produced prompt relief from all symptoms. The treatment, whether spinal drainage or surgical exposure, depends entirely on the character of the pathologic process. It is possible that all the various pathologic changes that have been described in the meninges are related to each other and vary only in degree. Davis and Haven recognized this fact and described cases of arachnoiditis according to three different types of meningeal changes: (1) inflammatory, (2) fibrotic and (3) hyperplastic. In the first group one can assume that there is a tremendous outpouring of spinal fluid into the subarachnoid spaces, which on histologic examination of the arachnoid show definite inflammatory exudate. The case reported here probably belongs to this group in the acute phase. The pleocytosis in the spinal fluid indicates an active meningeal process, and the meningeal fibrosis and marginal gliosis ten months later show evidence of the former inflammatory involvement. It may also be assumed that either this inflammatory phase may show a complete recession without producing any symptoms, as in the case reported here, or, as a result of a healing process plus a persistent chronic irritation, adhesions of the arachnoid with the formation of a cyst may result; it is this type of change that requires surgical intervention. That severe fibrosis of the meninges can be present without producing clinical symptoms is well borne out by the present case, since the patient was in good health prior to the accident.

As to etiology, there was nothing in this case to indicate any infectious process, although the leukocyte count suggests some infection. While it is possible that the meningeal involvement was a primary inflammatory process, this is not probable. From the recorded cases there is considerable evidence to suggest some infectious agent as a responsible factor. In a case under observation at present at the Temple University Hospital, as well as in 2 cases in the series reported by Craig and Lillie, and also by Frazier, "influenza" or some infectious process could be traced directly to the clinical picture of pseudotumor. In a number of instances trauma is unquestionably an etiologic factor. In many cases, however, no cause can be found.

Conclusions.—1. From a study of this case and a brief review of the literature, pseudotumor cerebri, although a poor term, should be used to indicate many pathologic processes the clinical features of which cannot be distinguished from the syndrome of tumor of the brain.

2. The condition may begin with psychotic manifestations that simulate a true psychosis.

3. The encephalogram may show either absence of the cortical pathways or tremendous dilatation of the channels.

4. Drainage of the spinal fluid in a selected group of cases may result in prompt and permanent cure and should be tried before surgical measures are attempted.

5. The various pathologic conditions that have been described are probably related and are variations in degree of the same process.

6. The character of the pathologic process determines the clinical picture and the method of treatment.

7. The histopathologic picture in the case reported was that of severe fibrosis of the meninges, marginal gliosis and an old sclerotic process in the Sommer sector of the cornu ammonis.

DISCUSSION

DR. NICHOLAS GOTTEN: Dr. Silverstein uses the term plastic arachnoiditis as applied to this symptom complex. This term is used most frequently by roentgenologists and is usually applied to cases in which an encephalogram has been made but in which there is absence of air over the cortex. There are some variations of opinion as to what is meant by the condition, if there is really such a condition. Dr. Chamberlain, of Temple University, recognizes plastic arachnoiditis as absence of air over the convolutions and thinks that the condition may be present even though there is air in the sulci. Dr. Dyke, of the Neurological Institute, refuses to admit that there is any such condition as plastic arachnoiditis. Dr. Sosman, who has previously stated that he did not believe there was such a condition as plastic arachnoiditis, today, told me that he was undecided about the condition. At Temple University operation has been performed in 3 cases in which roentgenologists had made a diagnosis of plastic arachnoiditis. In 2 the meninges were plastered down, not only over the convolutions but also into the sulci, and no fluid was found in that portion of the meninges. In other cases in which there have been definite thickening and adhesions of the meninges I have seen no fluid present in large quantities. There is no doubt in my mind, however, that this term is badly abused and that it may cause one to do some loose thinking if he is inclined to be satisfied with this diagnosis. Dr. Silverstein has pointed out the chances of error in using the term pseudotumor. I wish to make a much stronger statement. I do not think that the term pseudotumor means anything at all. If it does, it indicates merely that one has not made a diagnosis and that the symptoms presented are those frequently observed with increase of intracranial pressure. In most cases of pseudotumor there is meningeal involvement; this is most likely the cause of the symptoms. The symptoms may be due either to increase in the production of cerebrospinal fluid or to slowing of the rate of absorption of the fluid, or to both conditions. The increase in formation or decrease in the rate of absorption causes an increase in intracranial pressure with decrease of the blood supply of the brain, both locally and generally. The increase in intra-

cranial pressure with decrease in cerebral blood supply is sufficient, I think, to cause symptoms of tumor of the brain. Most patients improve rapidly following drainage of cerebrospinal fluid, whether by lumbar puncture, by ventricular puncture or by subtemporal decompression. The rapid improvement is due to increase in the blood supply of the brain or to removal of the cerebrospinal fluid. It is also possible that drainage of the cerebrospinal fluid helps to readjust absorbing powers. There can, I think, be no other explanation of the rapid improvement that these patients show following these procedures.

Dr. M. T. Moore: I think that the encephalogram shown here indicates the need for a more appropriate term than plastic arachnoiditis. The term implies the presence of an inflammatory process; yet in many such cases no inflammation has existed or does exist. The term arachnoid adhesions is more descriptive when the absence of air markings is due to proliferative changes in the pia-arachnoid. The ground glass appearance shown by these films does not necessarily imply that a definite cortical atrophy does not exist. At the Norristown State Hospital, where encephalography is carried out on psychopathic persons, encephalograms with the ground glass appearance, indicating an absence of air over the cortex, were often obtained in cases of peripheral vasomotor disturbances and dysfunction of the autonomic nervous system. The absence of air over the cortex indicates a disturbance in drainage of the cerebrospinal fluid from the cortical sulci, which may be due to one or more of the following factors: (1) arachnoid adhesions so situated as to produce a block preventing the egress of fluid and the ingress of air; (2) a change in the consistency of the cerebrospinal fluid, in which case the gelatinous material cannot be replaced by air, and (3) vascular engorgement and edema incident to the rapid exchange of cerebrospinal fluid and air, seen particularly in the patients with disturbance of the autonomic nervous system producing mechanical block of the cerebrospinal fluid pathways and hence the ground glass appearance. The term plastic arachnoiditis should be supplanted by one that will not be misleading.

Dr. Bernard J. Alpers: Dr. Moore asked for a term which would adequately describe these cases. I wish to suggest roentgen arachnoiditis, for the term arachnoiditis has been sadly abused since the encephalographic era to explain any and all situations in which air is not found over the cortex. What a roentgenologist calls arachnoiditis is usually unattended with clinical symptoms. The air fails to enter the cortical pathways in these cases, often because of absence of drainage. Usually it indicates no pathologic condition. The term pseudotumor, I think, usually includes a heterogeneous group of cases which are characterized by increased pressure and vague symptoms suggesting tumor but which cannot positively be classified as instances of tumor.

Dr. M. J. Cooper: I was particularly interested in Dr. Silverstein's account of the autonomic manifestations in his case and wish to ask him if the arachnoiditis found at autopsy was particularly pronounced in any one location as compared with other locations. Is it possible to correlate the clinical autonomic symptoms with the localization of the lesions as demonstrated at autopsy? A patient is now being studied at the University Hospital who gives a history of periodic attacks of marked sweating of bilateral distribution, chills alternating with flushing of the skin and presumably with increased body temperature, vomiting and profuse evacuation of the bowels, each of the attacks lasting twelve hours or more. There is moderate generalized arteriosclerosis, but investigations thus far have not revealed any distinct localizing signs. The men who are studying the patient hesitate to make a diagnosis of intraventricular neoplasm in this case, and injection of air is purposely being postponed.

Dr. Alexander Silverstein: Dr. Cooper wishes to know the correlation between the vasomotor disturbance and the histopathologic changes. The outstanding vasomotor disturbance was the unilateral sweating of the right side of the body during and following the convulsive seizure. In the case reported there were only very mild symptoms on the right side for a few days, indicating a cerebral

lesion in the left hemisphere, but this was entirely temporary, since all the symptoms disappeared after spinal drainage. The patient was in good health until sudden death from tetanus. At autopsy, more than ten months after the onset, a severe grade of meningeal fibrosis that was general and not localized was found.

In reply to Dr. Alpers' question whether pseudotumor is an advisable term, Bailey, in 1920, raised the same question. His conclusion was that if the term is to be used at all it should be for purposes of classification. Frazier used the term pseudotumor to classify his four groups of cases. In Nonne's original monograph the term pseudotumor indicated a definite clinical entity. At present the term pseudotumor, although a poor one, appears to be the most appropriate name to indicate the clinical picture.

As to the roentgenologic diagnosis of arachnoiditis from the encephalogram, it is true that, owing to incomplete drainage, there may be produced a picture in the encephalogram that can be interpreted as arachnoiditis. I have been able to follow up some of these so-called cases of arachnoiditis at operation and post mortem without finding any suggestion of the pathologic condition that was apparently present in the encephalogram.

News and Comment

COMMITTEE FOR THE STUDY OF SEX VARIANTS

During the spring of 1935 a committee for the study of sex variants was formed with the following membership: Eugen Kahn, M.D., Yale University, chairman; Robert W. Laidlaw, M.D., Columbia University, secretary, and Carney Landis, Ph.D., Columbia University, treasurer. These three officers, together with Robert L. Dickinson, M.D., National Committee on Maternal Health, and Josephine H. Kenyon, M.D., Columbia University, constitute the Executive Committee. The committee members are Clarence O. Cheney, M.D., Columbia University; Maurice R. Davie, Ph.D., Yale University; Earl T. Engle, Ph.D., Columbia University; George W. Henry, M.D., Cornell University; E. A. Hooton, Ph.D., Harvard University; Marion E. Kenworthy, M.D., New York School of Social Research; K. S. Lashley, Ph.D., Harvard University; Adolf Meyer, M.D., Johns Hopkins University; Catharine Cox Miles, Ph.D., Yale University; Harold D. Palmer, M.D., University of Pennsylvania; Philip E. Smith, Ph.D., Columbia University; Edward A. Strecker, M.D., University of Pennsylvania; Lewis M. Terman, Ph.D., Stanford University, and Dorothy S. Thomas, Ph.D., Yale University.

The objects and reasons for the organization of this committee are: (1) to correlate the various scientific interests in this field of study; (2) to serve as a scientific sponsoring agency for the furtherance of research on sexual variation, and (3) to appoint advisory subcommittees for projects sponsored or to be sponsored by the committee.

At the present time the committee is sponsoring several projects dealing with homosexuality as it appears in various classes of society. A study of fifty homosexual males and fifty homosexual females of cultured background is already under way. Plans are far advanced for: (1) a study of homosexuality as it exists among members of the United States Marine Corps, and (2) a study of homosexual practices among adolescent boys who are inmates of an institution for juvenile delinquency. These projects include a psychiatric, endocrinologic, roentgenologic and hormonal approach to the problem.

The committee will be glad to consider any research projects which may be presented that have a bearing on the physiologic, psychologic, psychiatric or sociologic problems of sex variants and to act in a sponsoring and advisory capacity should such projects be approved.

All communications should be addressed to the secretary at 199 Fort Washington Avenue, New York.

Book Reviews

Ueber Multiple Sklerose; exogene Aetiologie, Pathogenese und Verlauf. By Rudolf von Hoesslin. Paper. Price, 5 marks. Pp. 101. Munich: J. F. Lehmann, 1934.

This little monograph, by a veteran neurologist, is based on an extensive survey of the literature and a study of the records of 516 cases from the larger hospital of Munich. Especial attention is paid to the older accounts, now too often forgotten. Although there are minor errors and omissions in the review (Cramer's case is credited to Wolf, Schlesinger's important observation is not mentioned, and the recent developments in this country are omitted), the enormous preponderance of evidence in favor of the influence of exogenous factors stands out clearly. A hereditary predisposition is more vaguely suggested by certain cases.

The series of cases which the author has reviewed personally are well classified, and a few of them are concisely abstracted. In 17.4 per cent of the cases the first symptoms were observed in the fifth decade or later. The disease was fatal within two years in 221 of 509 cases, but was protracted for fifteen years or more in 51 cases. One patient lived fifty-one years after the onset of symptoms. One or more remissions occurred in 17 per cent of the cases, occasionally lasting from ten to twenty years.

In 27 cases a sudden, often apoplectiform, onset without a known external cause was recorded. In 36 cases an acute onset immediately followed various forms of trauma (including operations). In 18 cases the sudden onset was preceded by a febrile illness, in 8 cases by overexertion, in 7 cases by exposure to cold, in 7 cases by pregnancy and in 5 by emotional excitement. In 53 further cases, similar exogenous factors appeared to precipitate relapses or mild, slowly progressive symptoms.

Von Hoesslin concludes that multiple sclerosis is a disease caused by exogenous factors, and that at most only the predisposition is hereditary. There appears to be a close relationship to myelitis. Many types of trauma appear to precipitate the disease, not alone injuries to the head or spine. The author believes that the cause is an unknown virus, though there is some evidence that the etiologic substance may arise within the body.

Diffuse Sclerosis: Encephalitis Periaxialis Diffusa. By L. Bouman, M.D. Price, $5. Pp. 160, with 64 illustrations. Baltimore: William Wood & Company, 1934.

Bouman, one of the foremost neurologists of Netherlands, has written in English a monograph bringing together a large number of cases of Schilder's disease and allied conditions from the literature and reporting in detail six of his own. There is a fine bibliography at the end, together with a tabulation of cases that serves to emphasize the points that he makes.

In the first place, Bouman states, the classic features of diffuse sclerosis—cortical blindness, mental changes and progressive spasticity—do not hold for all cases, although they may be the terminal state in a large percentage. He considers mental changes to be of outstanding importance and of great significance in differentiating this condition from disseminated sclerosis. Many of the patients found to have diffuse sclerosis have been operated on for suspected tumor, although here again the psychic symptoms are apt to be out of proportion to the symptoms of general pressure. In children difficulties may be encountered in distinguishing Schilder's disease from the Pelizaeus-Merzbacher disease and also from amaurotic idiocy. Both these diseases are familial, but sometimes Schilder's disease is also

familial. Bouman divides the cases into those appearing before the age of 15 and those in adolescents and adults, since there are rather marked differences in these types. Spasticity seldom appears in later life in such intensity as it does earlier. The author gives a splendid presentation of the pathologic aspects of the subject on the basis of his own cases, pointing out the rather irregular distribution of the lesions, their sharp limitation in most cases to the white matter and the variable amount of reaction and gliosis that takes place. His points are illustrated by excellent photographs of sections.

Concerning the nature of the disease, the author is conservative and, while pointing out many resemblances of the disease process to that found in disseminated sclerosis, draws attention to differences in the pathologic picture, leaving the reader to draw his own conclusions. Chapter 5, dealing with debatable pathologic points, is particularly illuminating in this regard. Unfortunately for the sufferers from the disease, the author is unable to devote more than three lines to therapy. Bouman has treated the subject in a thoroughly scholarly manner, and the publishers have presented his work in pleasing form.

Book Notices

La syphilis du cervelet et des connexions cérébelleuses. By J. Thiers. Price, 20 francs. Pp. 104. Paris: Gaston Doin & Cie, 1934.

This monograph is of interest particularly for one wishing to find out what the French really mean by cerebellopyramidal and cerebellothalamic syndromes. Otherwise it is not particularly convincing. No specific mention is made of the syndrome resulting from occlusion of the anterior superior cerebellar artery, nor is there anything significant dealing with the cerebellar symptoms observed in dementia paralytica or the explanation for the tremors or dysarthria observed in patients with this disease; indeed, the latest reference in this section dates back to 1920. The volume is carelessly written and has few adequate photographs, their place being taken by some highly schematic drawings; the photographs that are reproduced are decidedly inferior. It is strange that ataxia should still be considered as due to disorders of the cerebellum in the presence of loss of both motor and sensory functions.

Hirnpathologische Beiträge. By K. Schaffer and D. Miskolczy. Volume 14. 1934.

This, the fourteenth volume of the collected works of the neurologic and psychiatric institutes in Budapest and Szeged, is dedicated to Prof. K. Schaffer on his seventieth birthday. It is composed of collected papers from these laboratories and clinics published during 1934. Nonne has written an appreciation of Schaffer, and Ramón y Cajal contributed an article on the neuron theory. The subjects discussed cover a wide field and are indicative of Schaffer's broad interests. The volume is of the same high standard of excellence as the previous studies from these internationally famous clinics.

The Biological Concept of Man: A Brief Introduction. By A. H. Miller, M.D. Pp. 34.

This pamphlet, probably privately printed, tries to introduce some involved concept of man and of diagnosis of disease. The work is highly philosophical and not very understandable and seems to have no practical connection with anything concrete in the fields that it mentions.